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ROENTGEN CONTRAST DIAGNOSIS OF EXPERIMENTAL MITRAL AND AORTIC INSUFFICIENCY IN DOGS BY TRANSVENTRICULAR INJECTION AND RETROGRADE CATHETERIZATION

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RECENT advances in cardiac surgery have served to emphasize the need for greater precision in the clinical diagnosis of valvular lesions of the heart. Physical diagnostic methods, electrocardiography, electrokymography, cardiac catheterization, and even direct pressure tracings from the heart[1] may all fail to disclose the existence of significant mitral insufficiency, particularly when this lesion is combined with mitral stenosis. The surgeon's finger itself may in some instances be incapable of estimating the degree of mitral insufficiency.[2] With the steady increase in the amount of aortic valvular surgery being performed, the more accurate demonstration of the anatomic and functional details of aortic valve lesions becomes essential.

Experimental visualization of the dog ventricle by direct injection of contrast medium was performed first in 1933 by Reboul and Racine,[3] utilizing an intercostal needle. In 1936, Nuvoli,[4] using the same approach, injected sodium iodide solution into the left ventricle of a patient with an aortic aneurysm. In 1945, Radner[5] visualized the coronary arteries in man by direct puncture of the ascending aorta through the sternum. In 1951, Nunēz and Ponsdomenech[6, 7] coined the term "cardioangiography" for the direct injection of contrast media into the chambers of the human heart. They studied 30 patients in this manner without mortality and made the diagnosis of mitral insufficiency when radiopaque material was noted to reflux into the

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left atrium after direct injection into the left ventricle. Smith and co-workers[8] repeated these studies in 18 dogs and in 6 human beings. They were able to demonstrate mitral insufficiency in one patient. In another patient, an episode of ventricular fibrillation followed the intraventricular injection of 70 per cent Diodrast, requiring cardiac massage for resuscitation. In a later report, these workers inferred that the degree of insufficiency found by this cardioangiographic method correlated closely with the anatomic findings as found at surgery. Björk and his colleagues[16] have injected contrast medium into the left atrium by means of a plastic catheter threaded through a thoracentesis needle passed paravertebrally into the left atrium. Severe reactions occurred following this procedure and in no case was it possible to inject contrast substance into the left ventricle because of catheter recoil. Kjellberg and co-workers,[17] utilizing venous catheterization, have injected contrast medium into the left atrium and left ventricle of patients with congenital septal defects.

The contrast visualization of the proximal aorta has been carried out through retrograde arterial catheterization or retrograde arterial injection by many workers. Castellanos and Pereiras,[10] in 1939, visualized the aortic valve in patients by means of retrograde injection of the left brachial artery. In 1948, Radner[11] performed retrograde catheterization of the human aorta via the radial artery, and Jönsson and his co-workers,[12] in the same year, visualized a patent ductus arteriosus by this method. Other workers have used the carotid artery to perform thoracic aortography.[13, 14] Katz and colleagues,[15] in 1947, obtained excellent contrast studies of the coronary circulation and aortic valves in dogs, using retrograde aortic catheterization. Boerema and Blickman[18] have utilized increased intrabronchial pressure as a means of slowing the circulation of the injected dye through the heart and have published unusually clear angiograms of the normal aortic valves in the dog.

This communication undertakes to describe the results of two methods for the roentgen contrast demonstration of insufficiency of the mitral and aortic valves. Direct puncture of the left ventricle, and retrograde aortic and left ventricular catheterization were the techniques utilized. The possible application of these techniques for the diagnosis of valvular disease in man is discussed.

METHOD

Mongrel dogs weighing 12 to 21 Kg. were used. They were lightly anesthetized with intravenous veterinary Nembutal and placed on the x-ray table in the right lateral position. Single spot roentgenograms were made using 120 kv. and 300 Ma. at $\frac{1}{30}$ to $\frac{1}{10}$ second depending on the size of the dog.

A total of 158 contrast radiographic studies were carried out in 38 dogs. One hundred and seventeen of these were performed by the direct injection of 70 per cent Urokon into the left ventricle, as described by Nunëz and Ponsdomenech.[6] A 5½-inch No. 18 needle was passed through the skin just below the xyphoid process. The needle was directed in a cephalad direction, parallel to the sternum and slightly to the left of the midline. The needle was advanced 1 inch after the cardiac impulse was felt. Appearance of

oxygenated blood confirmed entrance into the left heart. A plastic connecting tube and a syringe, filled with 1 to 1.5 c.c. of 70 per cent Urokon, was attached to the needle. The material was injected by hand as rapidly as possible, usually requiring from 1 to 3 sec. At or near the completion of the injection, a single roentgenogram was taken and the needle was immediately withdrawn.

The remaining 41 injections of Urokon were carried out using a No. 9 Lehman aortic x-ray catheter. Under fluoroscopic control, the catheter was passed retrograde through an incision in the femoral artery, into the aorta, and positioned either above the aortic valve or in the left ventricle. When the tip of the catheter approached the aortic valve slight resistance was often encountered. With a minimum of manipulation the catheter could easily be slipped by the valve. The catheter was attached to a 3-way stopcock with a plastic connecting tube and a syringe containing the contrast medium at one port, and an intravenous unit containing isotonic saline and 10 mg. of heparin per 500 c.c., to flush the catheter, at the other. Once in position, either in the apex of the left ventricle or above the aortic valve, the radiopaque medium was injected and a single spot roentgenogram made. After the completion of one or more injections, the catheter was withdrawn. The femoral artery of the dog could be successfully repaired in many cases.

During production of the desired valvular lesions, dogs were anesthetized with intravenous Nembutal (60 mg. per 5 pounds of body weight). An endotracheal tube was inserted and attached to a positive-pressure pneophore respirator supplying 100 per cent oxygen. The left chest was entered through the fourth or fifth intercostal space. A nerve hook was passed into the left ventricle through the ventricular myocardium. To produce mitral insufficiency, a finger was inserted into the left atrium and the nerve hook guided so that the posterior leaflet of the mitral valve was torn. Aortic insufficiency was produced by first directing a nerve hook through the left ventricle into the aorta. As the hook was pulled back into the ventricle, an aortic leaflet was caught and ruptured. Mitral stenosis was created by passing a ligature in the plane of the interatrial septum at the level of the atrioventricular valves and then tightening it around the mitral valve, either above or below the annulus. After the production of the various valvular lesions, the chest was closed and the dog allowed to recover before x-ray procedures were carried out.

RESULTS

The Normal Left Heart.—Roentgenograms of the normal heart recorded during the injection of the contrast medium into the left ventricle by direct heart puncture (Fig. 1) and by retrograde arterial catheterization (Fig. 2) demonstrate the roentgen anatomy of the left heart in dogs as seen in the right lateral position. With either technique, the left ventricle, the aortic valves, the sinuses of Valsalva, the aorta, and usually the coronary arteries can be seen (Fig. 3). To the right and inferior to the base of the aorta, the contrast medium in the left ventricle ends abruptly, forming a sharp crescent-shaped

Fig. 1.—Roentgenogram following direct needle puncture and injection of Urokon into left ventricle of a normal dog. The needle is seen entering the left ventricle from below. The competent mitral valve prevents regurgitation of the contrast medium into the left atrium.

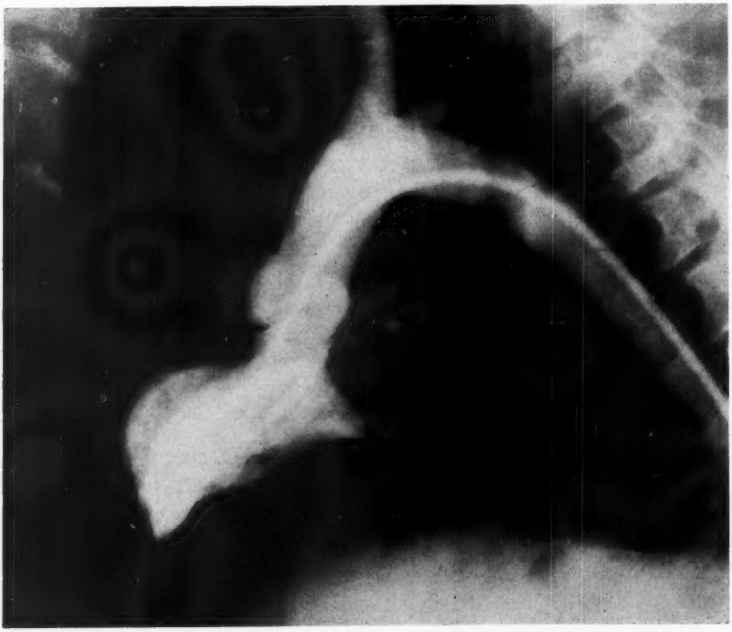


Fig. 2.—Retrograde catheterization of the left ventricle of a normal dog and dye injection through a No. 9 Lehman aortic catheter. The left ventricle, mitral valve area, sinuses of Valsalva, and a coronary artery branch are visualized. No dye has refluxed into the left atrium.

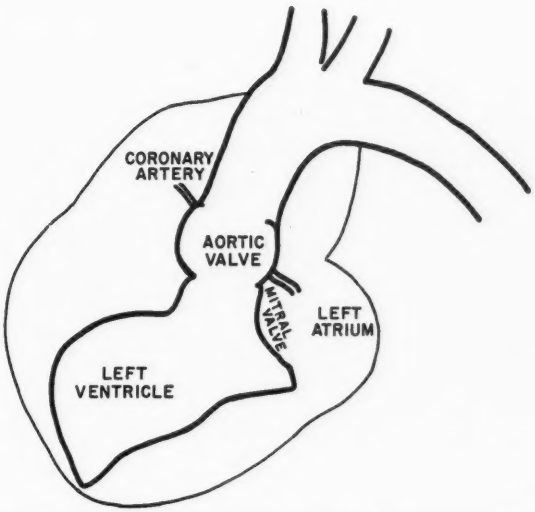


Fig. 3.—Diagrammatic representation of anatomic details of roentgenogram shown in Fig. 2.

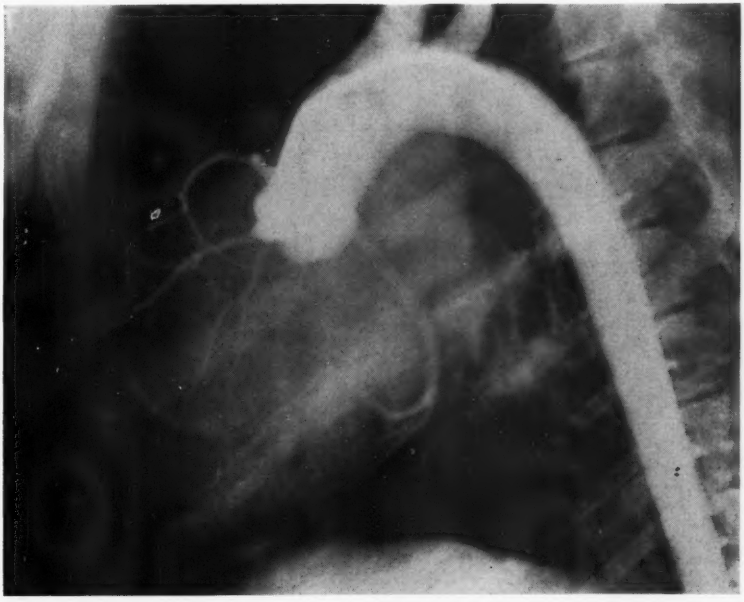


Fig. 4.—The anatomy of the normal dog aortic valve and arch following injection of 70 per cent Urokon through a retrograde catheter with tip in ascending aorta. No dye is seen in the left ventricle.

border. This margin represents the closed mitral valve. The normal competent mitral valve prevents visualization of the left atrium which lies just posterior to this sharp crescent-shaped border. In this projection, the valve lies so that the posteromedial commissure is at the base of the aorta and the anterolateral commissure opposite. The outline of the ventricle is sharp and the entire ventricle is filled with contrast medium. The contour of the ventricular chamber differs depending on whether the film is taken in systole or diastole. Visualization of the aortic valve leaflets and the bulging sinuses of Valsalva is especially clear.

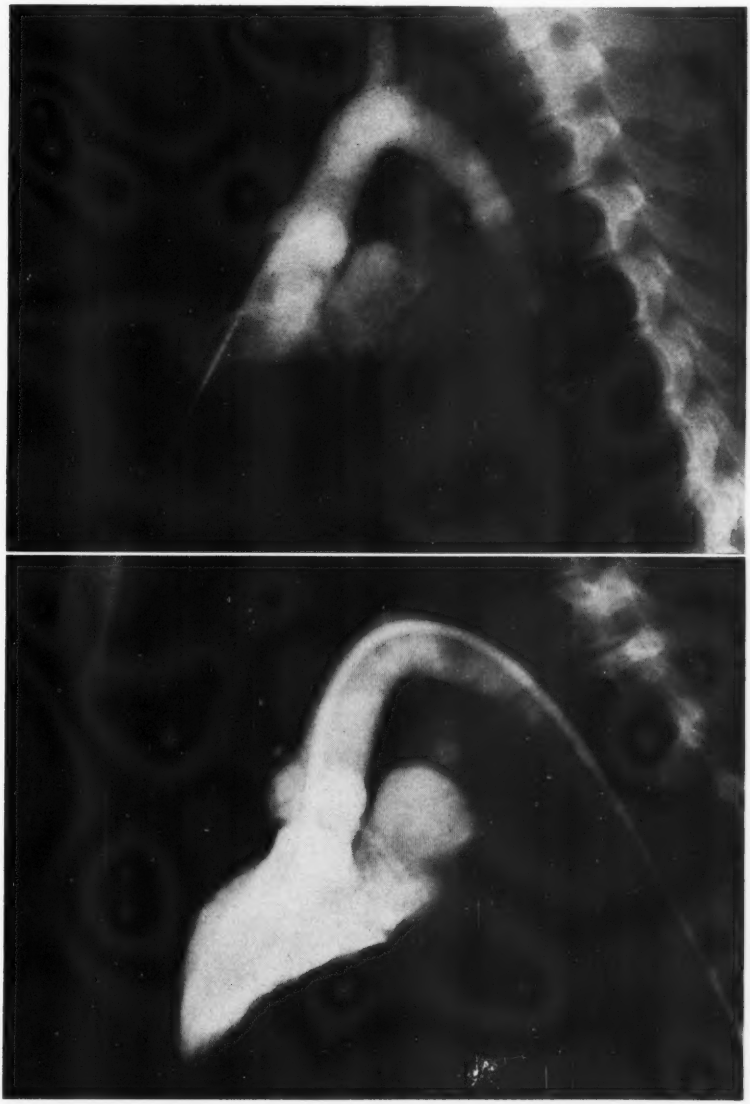
When radiopaque material is injected into the ascending aorta through an arterial catheter, the sinuses of Valsalva, the coronary arteries, and the aortic valve leaflets are sharply visualized. No dye is seen in the left ventricle (Fig. 4). In a series of 19 injections of contrast medium into the left ventricle by both techniques, and ten injections of contrast medium into the ascending aorta by retrograde arterial catheterization, complete competency of the mitral and aortic valves in normal dogs was demonstrated.

The Heart in Mitral Insufficiency.—In 20 of the 38 dogs studied, mitral insufficiency was created as described and radiographic studies recorded. Fig. 5, *A* and *B*, demonstrates the results of direct and of retrograde injection of contrast medium into the left ventricle of 2 dogs with experimental mitral insufficiency. Because of the damaged mitral valve, the dye regurgitates freely into the left auricle. The retrograde arterial catheter makes it possible to inject a greater volume of dye more rapidly than by the needle technique, and a denser roentgenogram results.

Chronic Mitral Insufficiency.—Serial x-rays obtained over a period of one year in a dog with chronic mitral insufficiency are illustrated in Fig. 6. The increasing size of the auricle is apparent by either of the two techniques of injection. In some animals, the insufficient mitral valve in time becomes competent once again by the heaping up of granulation and fibrous tissue at the edges of the operative lesion. Fig. 7 demonstrates the x-ray films of a dog, 2 months, 5 months, and 7 months after the creation of a small mitral insufficiency. The x-ray at 7 months was interpreted as showing no regurgitation and the dog was then re-explored. No apparent regurgitation could be detected at that time either by digital examination or by pressure recordings from the left atrium. Post-mortem examination revealed the lesion in the posterior leaf of the mitral valve to be healed by fibrosis around the edges of the previous valve rupture. Fig. 8 illustrates examples of marked mitral insufficiency of 6 months' duration in 2 dogs using both techniques of injection.

The group of 20 dogs, with experimentally produced mitral insufficiency, were followed with serial radiographic studies at two- to three-month intervals by direct and retrograde injection of contrast material. In all cases, where two or more successive x-rays revealed that mitral insufficiency no longer existed, a second operation confirmed the presence of a competent valve. There were 3 dogs in which two consecutive x-rays were inconclusive. At operation a small regurgitant jet could be intermittently felt in 1 and a small but definite

A.



B.

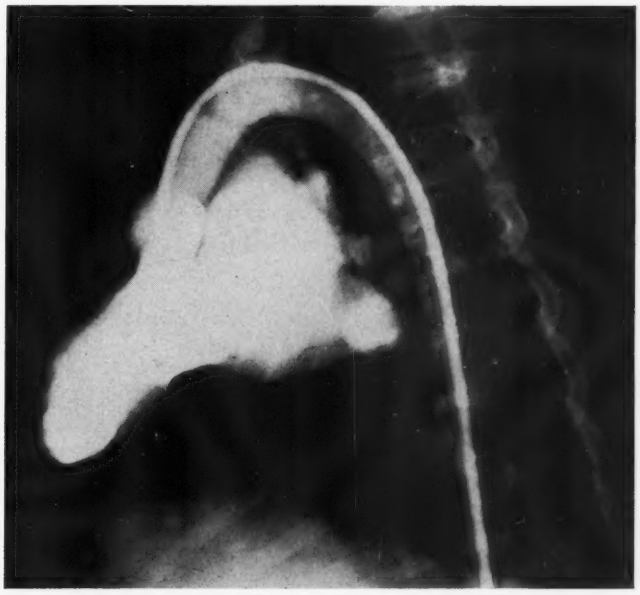
Fig. 5.—The roentgen appearance of the dog heart with experimentally produced mitral insufficiency. Free reflux of dye into the left atrium through the incompetent mitral valve is seen after left ventricular injection. *A*, direct needle puncture of left ventricle. *B*, retrograde catheterization of left ventricle.

A.

B.

Fig. 6.—A series of left ventricular dye injections in a dog with chronic mitral insufficiency over the course of one year. Note the progressive left atrial and pulmonary vein dilatation. *A*, postoperatively; *B*, 6 months later.

regurgitant jet could be felt in 2. There was no obvious change in the left atrial pressure curve in any of these 3 cases. Of the other 17 dogs, 4 had no mitral insufficiency, two to six months postoperatively, as demonstrated by x-ray and confirmed at re-exploration. There were 13 dogs with varying degrees of insufficiency demonstrable by dye injection, which persisted for as long as 15 months after the creation of mitral insufficiency.

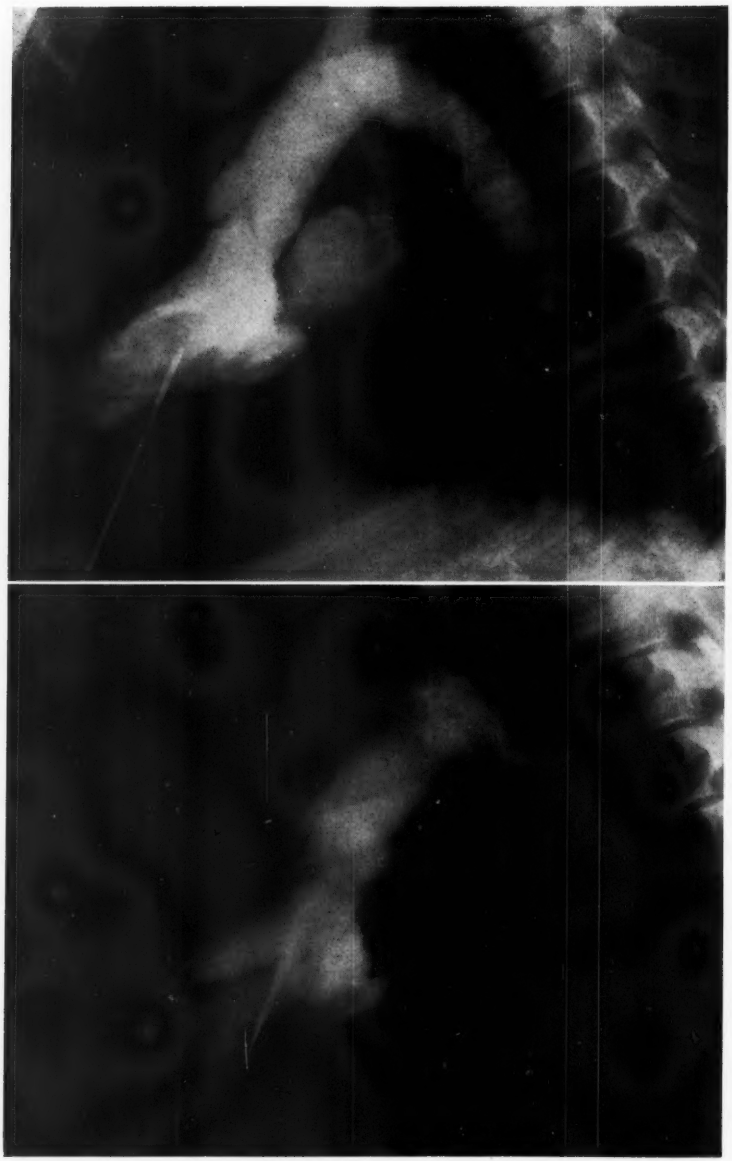


C.

Fig. 6—Cont'd. *C*, 1 year later.

Mitral Insufficiency and Mitral Stenosis.—The double valvular lesion of mitral stenosis and mitral insufficiency was produced and x-rays recorded in the manner described. Fig. 9 illustrates the roentgen appearance of the left cardiac chambers in dogs with combined mitral stenosis and mitral insufficiency. The size of the mitral orifice and the position of the experimental stenosis may be estimated from the films in many cases. In Fig. 9, *A*, the stenosing suture was passed around the atrium above the mitral annulus and the left circumflex coronary artery. In this film the constriction of the atrium just above the annulus is obvious. The stenosis is of moderate degree. Fig. 9, *B*, reveals the x-ray in a dog with severe mitral stenosis and moderate insufficiency. In this case, the stenosing suture was tightened in a plane just below the left circumflex coronary artery. The narrowing of the mitral valve area is clearly visualized. The left circumflex coronary artery appears to be uninvolved by the circumflex suture. Pressure tracings recorded at the time of the surgical production of mitral stenosis revealed evidence of a markedly elevated left atrioventricular diastolic pressure gradient. In Fig. 10, *A*, the x-ray reveals a

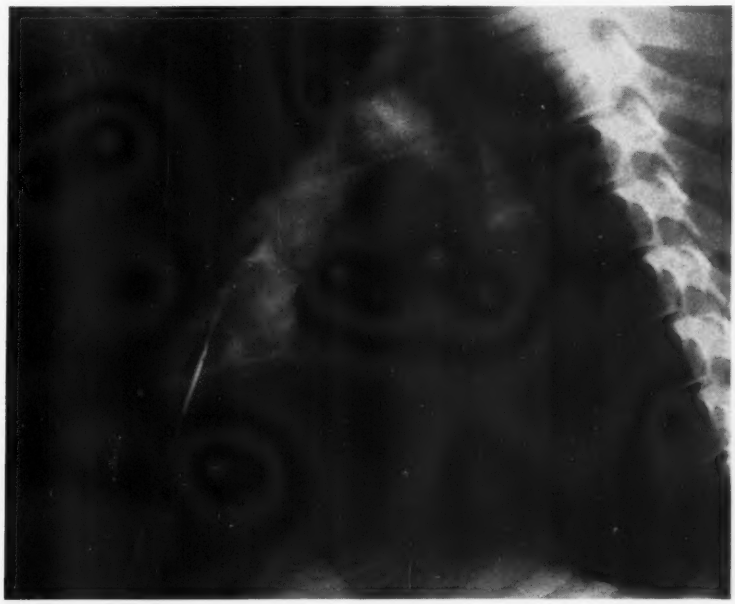
A.



B.

Fig. 7.—Spontaneous healing of experimentally produced mitral insufficiency. *A*, Two months postoperatively; *B*, 5 months postoperatively.

significant mitral insufficiency. In this animal, at a second operation, a stenosing suture was passed and tightened around the mitral ring below the annulus. A subsequent dye injection revealed apparent reduction in the amount of mitral regurgitation (Fig. 10, *B*). It should be noted that when a circumferential stenosing suture is passed around the mitral ring below the annulus, the course of the coronary artery may occasionally be modified and in Fig. 10, *B*, the buckling of the circumflex coronary artery is obvious.



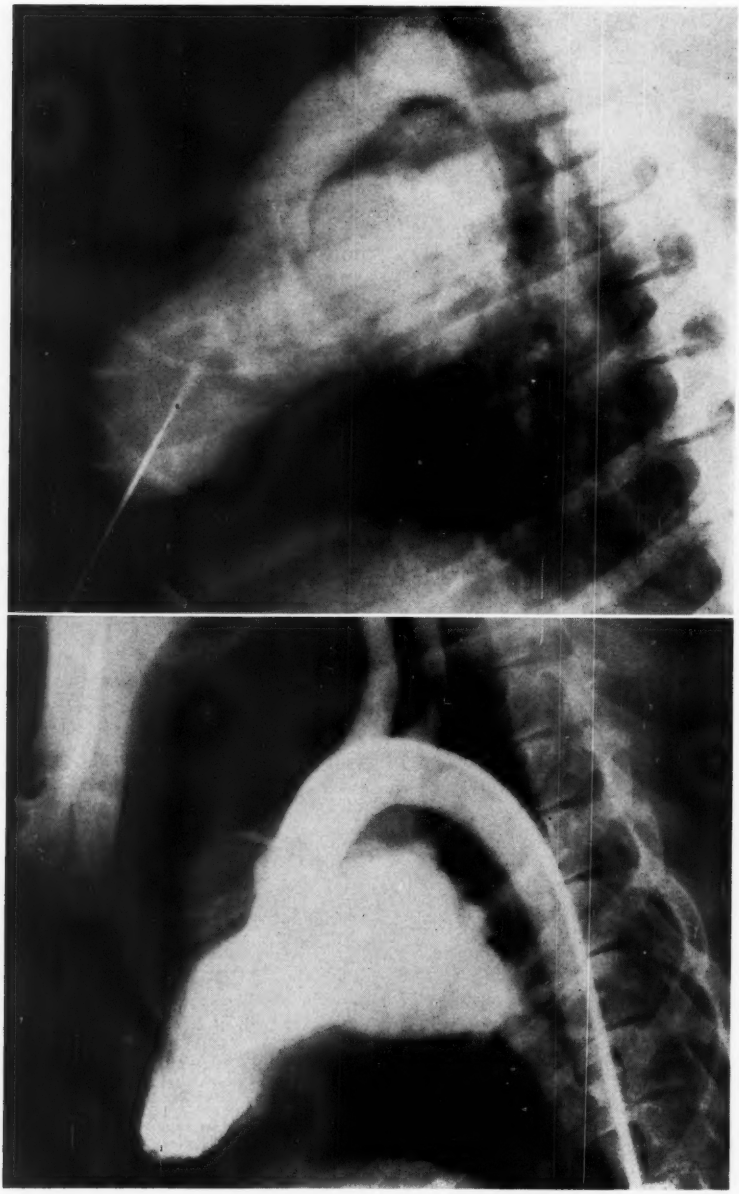
C.

Fig. 7.—Cont'd. *C*, 7 months postoperatively. The regurgitant jet of contrast medium has disappeared 7 months after the lesion was created. No mitral insufficiency could be detected at re-exploration or at post-mortem.

Aortic Insufficiency.—The normal aortic valve was studied by retrograde aortic catheterization and dye injection in 10 dogs. In 5 dogs, aortic insufficiency was produced and studied by the same technique. With a competent aortic valve as shown in Fig. 3, dye introduced into the ascending aorta outlines the aortic valve, sinuses of Valsalva, and the coronary arteries. No dye is seen in the left ventricle. Fig. 11 demonstrates the appearance of the roentgenogram in a dog with aortic insufficiency. Free reflux of the contrast medium into the left ventricle has taken place.

Cine-angiography.—The image intensifier makes it possible to record high-speed motion pictures of a fluoroscopic screen at the rate of 48 frames per second during the injection of radiopaque media into the ascending aorta, the left ventricle, and the left atrium. These motion pictures demonstrate the dynamic details of valvular anatomy and function both in the normal and in the experimentally altered state. The flow of dye from one cardiac chamber to another

A.



B.

Fig. 8.—Chronic mitral insufficiency of 6 months' duration. The considerable enlargement of the left atrium and dilatation of the pulmonary veins is apparent.

is clearly visualized as well as the motion of the valve leaflets. The mixing and diluting of the dye with blood graphically demonstrates the action of eddy currents in the heart chambers. Lesser degrees of aortic and mitral insufficiencies may be detected in this manner and this technique may yield additional information in localizing and determining the size of various valvular lesions.

A.

B.

Fig. 9.—Mitral stenosis and insufficiency. *A*, The stenosing circumferential mitral suture has moderately narrowed the left atrium above the mitral annulus. *B*, The suture has been passed just below the mitral annulus and has produced a high grade of stenosis. Mitral regurgitation is still readily visible despite the marked narrowing of the mitral orifice.

Complications.—In the over-all series of 38 dogs, no dog developed any permanent deleterious effect following a single intraventricular injection of the radiopaque medium. Bursts of premature ventricular contractions characteristically occurred at the time of the injection with a transient drop in blood pressure. However, when repeated and closely spaced injections were carried out, the dogs frequently developed serious arrhythmias, hypotension, and, in some cases, died.

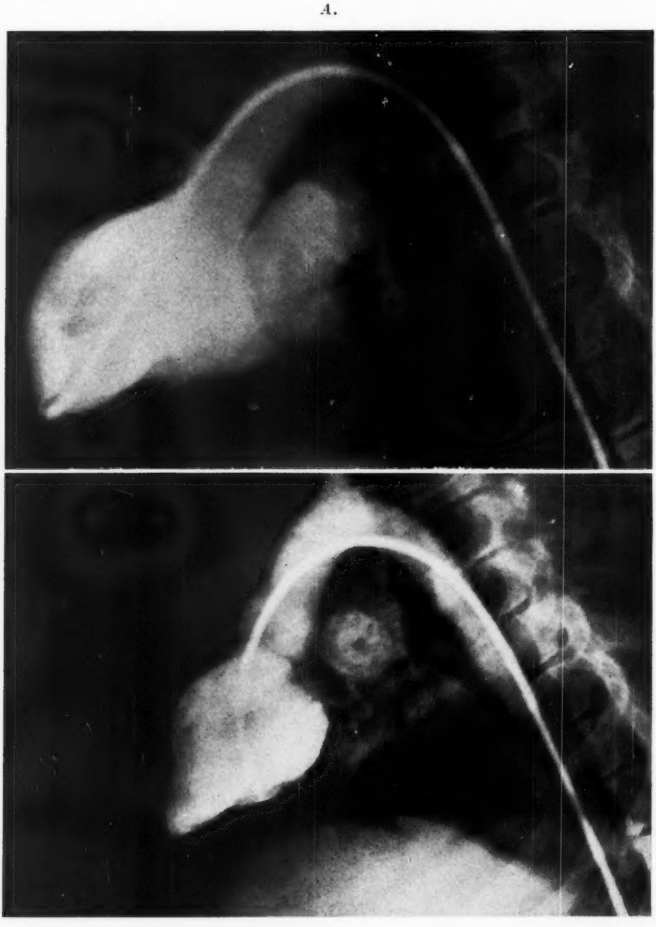


Fig. 10.—Mitral insufficiency and stenosis. *A*, The lesion of mitral insufficiency alone is shown. *B*, Two months later a moderately tight stenosing suture has been superimposed on the incompetent mitral valve. An apparent reduction in the degree of mitral regurgitation has taken place. Note the tortuosity of the left circumflex coronary artery produced by the mitral stenosis.

Approximately 91 direct injections and 20 retrograde injections into the left ventricle were carried out in the colony of 20 dogs with mitral insufficiency. These dogs were usually subjected to only one or two injections of contrast

medium during any one 24-hour period. In this long-term series, there were two fatalities with the direct injection technique and none using the retrograde catheter. The first fatality took place when the needle slipped back into the wall of the heart and 5 to 10 c.c. of dye was injected into the left ventricular myocardium (Fig. 12, *A*). The dog suffered a convulsion and died immediately. The second dog was found dead 30 minutes after the cardiac puncture and injection. Post-mortem examination revealed several hundred cubic centimeters of blood in the pleural cavities. No laceration could be found in the ventricular wall or in a coronary vessel to explain the bilateral hemothorax. The pericardium had been left widely open several months earlier at the creation of mitral insufficiency. In 2 other dogs, small amounts of dye in the ventricular myocardium were seen on the films although nothing untoward had been noted during the injection and both dogs survived.

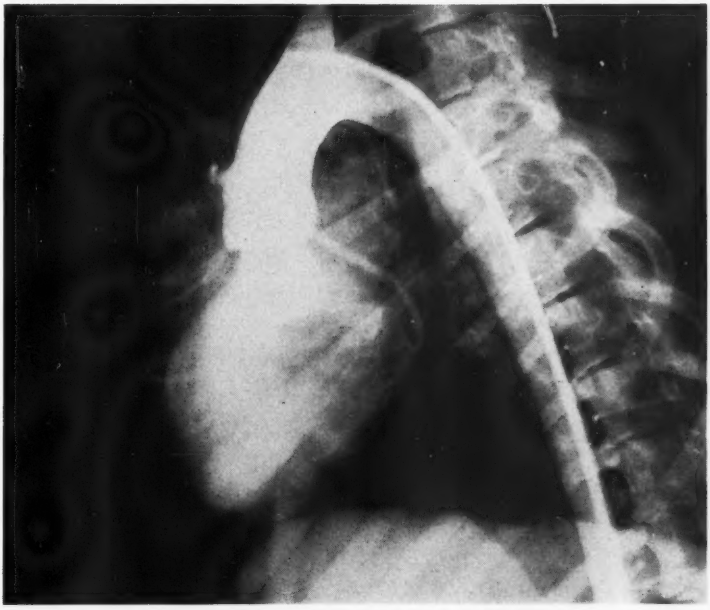


Fig. 11.—Aortic insufficiency. Dye injected into the ascending aorta freely regurgitates into the left ventricle through the torn aortic valve. Compare with competent aortic valve in Fig. 4.

In this series of dogs with chronic mitral insufficiency, the left ventricular punctures were made without fluoroscopic control and occasionally two or three attempts were required to enter the left ventricle. In a subsequent group of dogs, fluoroscopic control was used and this appears to be a useful aid in the correct positioning of the needle during direct puncture of the left ventricle. By injecting a small a small dose of Urokon under fluoroscopic observation, the position of the needle may be more precisely determined.

Electrocardiograms taken at the time of the direct puncture, and during the passage of the catheter through the aortic valve, have revealed frequent

A. *B.*

Fig. 12.—Complications of direct left ventricular puncture and dye injection. *A*, Intramyocardial extravasation of dye; *B*, accidental entrance of needle into coronary artery.

premature ventricular contractions. In the series of 17 injections of contrast medium in the ascending aorta, there was noted only transient effect on the electrocardiogram and no mortality.

COMMENTS

There appears to be little doubt that the normal mitral and aortic valves prevent regurgitation of injected radiopaque material during regular sinus rhythm. When these valves are rendered insufficient by the techniques used in this study, there has been no difficulty in recording either mitral or aortic reflux on a single roentgenogram. These experimental valvular lesions, however, differ from the lesions in the diseased valves of the human heart. Mitral insufficiency created in the dog by rupturing a valve leaflet is quite different from the lesion which results in man from the processes of shortening and thickening of the leaflets, or by dilatation of the mitral annulus. Aortic insufficiency experimentally produced in the dog by perforating an otherwise normal cusp has little anatomic correspondence to an incompetent aortic valve due to the scarring of the cusps and separation of the commissures. These important anatomic differences between the naturally occurring and the experimentally created valvular lesion may have corresponding functional variations. However, the essential feature of free retrograde reflux through the incompetent valve has been duplicated experimentally. It is this reflux which is responsible for the major hemodynamic change in mitral or aortic insufficiency and it appears clear that cardioangiographic technique detects its presence.

Quantitation of the degree of regurgitation is a much more difficult problem than the mere demonstration of its presence. Alterations in rate and contractility of the ventricle, changes in peripheral arterial pressure, variations in the speed of injection of the radiopaque medium, changes in roentgenographic technique, and transient arrhythmias at the time of injection, all may distinctly vary the density of the shadow of the regurgitating dye. Rapid dilution of the jet of dye in a large chamber may make the reflux appear smaller than an equivalent jet in a smaller cardiac chamber. A rise in arterial pressure head favors mitral reflux, while a transient episode of hypotension during the procedure could reduce the degree of regurgitation. Analysis of double outlet chambers has shown how significantly the speed of ventricular contraction may influence the degree of mitral reflux.[19] Any attempt at densitometric quantitation of the insufficiency must take into account these many factors. However, as can be seen from the illustrations (Figs. 6 and 7), large insufficiencies seem to give a denser opacification of the left atrium than do small ones, and there can be no doubt that the increasing size of the cardiac chambers is well demonstrated with this technique.

It is apparent from Figs. 5 and 9 that mitral insufficiency can be detected by this method when this valvular lesion exists alone or when it is associated with mitral stenosis. The stenotic valve actually prolongs circulation time through the left auricle and facilitates roentgen visualization of this chamber when mitral insufficiency and stenosis are combined. Since small regurgitant

jets may not be a contraindication to surgery in mitral stenosis, quantitation of the amount of reflux becomes an important consideration. As previously stated, it is our impression that a dynamically significant insufficiency usually gives a denser opacification of the left atrium than does a minor jet. In the series of radiographs in Fig. 7, the reduction in the size of a regurgitant jet is illustrated. The spot film technique, when adequately carried out with rapid injection and proper timing of the radiographic exposure, has not failed to demonstrate significant mitral insufficiency when present.

The transference of cardioangiographic technique for the diagnosis of mitral or aortic insufficiency to man would appear to depend primarily on the question of the safety of the procedure. Björk[16] described severe reactions after left atrial injection of dye. The two dogs that died in this study, and the patient in the report of Smith[8] who developed ventricular fibrillation, were all studied by the direct puncture technique. The major hazard of this needle technique would appear to be the inadvertent injection of the medium into the myocardium (Fig. 12, *A*), or laceration of a coronary vessel (Fig. 12, *B*). Neither of these complications can occur with retrograde arterial catheterization of the left ventricle. Accidental entrance of the retrograde catheter into a coronary orifice in man is a distinct possibility, but with careful fluoroscopy and attention to the electrocardiogram this should be avoidable. Fluoroscopic control will help avoid the hazard of passage of the catheter into a carotid artery and delivery of a large dose of contrast material to the brain. Injury to the aortic valve in passing the catheter into the ventricle may be avoided by gentle manipulation under fluoroscopy and by providing the retrograde catheter with a sharply curved tip. Arrhythmias encountered due to the introduction of the catheter into the aorta and left heart should be no greater than those met with in the right heart catheterization. However, it would appear that because of greater stability of the heart in the well-ventilated patient, the procedure should be carried out with an anesthetist in attendance, administration of 100 per cent oxygen just prior to the dye injection, and continued adequate oxygenation after the procedure.

Some of these conceivable complications are less likely to occur with dye injections through a catheter in the aorta for the demonstration of aortic insufficiency. In the present study, this type of injection was carried out without noticeable complication. It must be remembered that a virtually undiluted bolus of dye enters the coronary arteries during aortic injection and with preexisting coronary insufficiency this type of aortography has distinct potential hazards. Repeated and closely spaced contrast medium injections should be avoided. The problem of circulatory embarrassment to the limb in which the arterial catheterization is performed will be a real one unless careful preoperative assessment of collateral circulation and meticulous technique is observed. The radial artery has been used routinely in a large number of cases by Jönsson, Rrodén, and Karnell.[20] In adults, as shown by the experience of Peiree,[21] femoral catheterization with small catheters can be performed without danger to the limb.

SUMMARY

1. In dogs, the normal mitral and aortic valves prevent retrograde reflux of radiopaque contrast medium.

2. Mitral insufficiency is readily demonstrated on roentgenograms by the injection of contrast medium into the left ventricle, since the incompetent mitral valve permits reflux of dye into the left atrium.

3. Aortic insufficiency can be detected when contrast material, injected through a catheter in the ascending aorta, regurgitates into the left ventricle.

4. The combination of mitral stenosis and insufficiency is radiologically demonstrable by the injection of contrast material into the left ventricle.

5. The injection of contrast material into the left ventricle through the retrograde aortic catheter appears to be safer than the direct puncture technique.

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LUNG DENERVATION* IN THE THERAPY OF INTRACTABLE BRONCHIAL ASTHMA

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THE problem of the therapy of intractable bronchial asthma is well known. The use of ACTH, cortisone, and various antibiotics has meant a great advance when one considers the difficulty of attaining good results with the older drug therapy. However, after studying the earlier literature, it became clear that with the older treatment the serious condition of a number of asthmatic patients precluded anything more than symptomatic therapy. Following the asthmatic secondary changes, the patient's working ability steadily decreases, he becomes unable to work, and the prognosis is poor.

In order to treat bronchial asthma that resisted internal treatment, the idea of attacking the vegetative nervous system was tried long ago. First, in 1923, Kümmel obtained results with cervicothoracic sympathectomy, and, in 1924, Kappis with vagotomy on the right side. By the addition to the anatomic and pathophysiologic knowledge and the development of better techniques in thoracic surgery during the last three decades, several authors have dealt with the surgical treatment of intractable bronchial asthma and have tried to perfect the attack on the vegetative nervous system (Phillips, Scott, Leriche and Fontaine, Rienhoff and Gay, Miscall and Rovenstien, Carr and Chandler, Blades, Klassen, Abbott, and others).

In the Sebestény Clinic, after having tried and failed with every conservative treatment in a patient, we have then considered the possibility of surgical intervention in cases of intractable bronchial asthma as an "ultimum refugium" (Dimitrov-Szokodi).

The advisability and efficiency of the surgical treatment of bronchial asthma are still matters for discussion. In the literature, data concerning the theoretical basis of the various surgical procedures are also very contradictory. Therefore, before reaching a practical solution, it was essential to consider a few questions.

1. What is the role of the lung's extrinsic vegetative fibers in the pathology of bronchial asthma?

2. What kind of vegetative intervention seems to be anatomically and pathophysiologically best founded?

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*We mean by this, the bilateral intervention of extrinsic vagus and sympathetic nerves of the lung.

3. Can the "nil nocere" principle be followed when operating on the vegetative fibers of the lung?

1. In the pathogenesis of bronchial asthma, besides the ordinary features, we wish to emphasize the important role of the lung's allergic-infectious processes (Hajós and Hetényi, among others).

The question is, how can these processes lead to asthmatic attack? For the understanding of the pathomechanism of asthmatic attack we refer to Danielopolu's theory. According to this theory, the often recurring stimuli of the allergic and infectious processes (the release of "H-materials") taking place in the lung, lead to the excitation of the vegetative centers via afferent pathways. This stimulation is transferred to the lung by efferent pathways and it further increases the changes and damages. The developing bronchial spasm, swelling of the mucous membrane, hypersecretion, stasis of the pulmonary vascular system ([Tsuji] parasympathetic effects) create unfavorable conditions; the inhibition of expectoration leads to retention of the secretion, and to increase a tendency for infections, also. The mentioned changes caused by the efferent impulse, i.e., those chemical mediators (acetylcholine, histamine, etc.), released in the meantime, stimulate again the already more sensitive receptors. There is a vicious circle of reflex actions taking place between the vegetative centers and the lung. The extrinsic vegetative pathways of the lung play an important role in the communication of this reflex. After the development of this vicious circle, not only can the original cause lead to asthmatic attack, but a wide scale of other mild and shortlasting extero- and interoceptive stimuli (psychic, neural, humoral stimuli) also can produce a continuous vicious circle increase, which can be manifested in a longer asthmatic paroxysm.

On the basis of the research of Pavlov and his school, there is a possibility of developing conditioned reflexes owing to the frequent repetition of the attacks. The importance of conditioned reflexes in the asthmatic condition is supported also by our own clinical observations.

The pathologic role of the vegetative nervous system in asthma, caused either by allergic condition or by infection, becomes manifest also in numerous experimental studies. The experiments of Reitler, Friedberger, Bogendörfer, Moser and Tusch, Kiszelev and Migina, Filipp, Szentiványi and Mess, and others, proved that with the experimental lesion of the central parts of the vegetative nervous system (brain stem, tuber cinereum, etc.) the development of general anaphylactic-allergic signs can be prevented. On the other hand, the rise of local anaphylactic-allergic signs can be inhibited or greatly reduced in their intensity by the interruption of the peripheral vegetative innervation (Buchwald, Wyropajev, Keztyüs and his co-workers, among others).

Similar experimental results are obtained also with the prevention or reduction in intensity of the development of local infectious processes by the interruption of peripheral fibers (Szperanszkij, Mansfeld).

2. Our aim was to eliminate the pathologic role, just outlined, of the vegetative nervous system by surgical intervention in the case of intractable

bronchial asthma. It is necessary to give a short review of the lung's innervation for the determination of the suitable spot and extent of the operation.

The lung is innervated by the vagus and the sympathetic nerves, both of which contain afferent (sensory) and efferent (motor) fibers. From the vagus nerve the pulmonary branches arise on the portion extending from the origin of the recurrent nerve to the pulmonary ligament. The main sympathetic supply of the lung comes from fibers from the ganglia of the second to fifth thoracic vertebrae of the sympathetic chain (Braeucker, Kuntz, Kiss, Mitchell, Dijkstra). The vagus and the sympathetic nerves have an extensive anastomosis with each other and also with the contralateral similar fibers. Therefore, both lungs receive vagus and sympathetic fibers from the same as well as from the contralateral side. Thus, the lung's innervation is "bilateral and bisystematic" (White and Smithwick).

From the physiologic point of view, the vagus nerve cannot be considered to have only cholinergic effect and the innervation coming from the sympathetic chain to have only adrenergic effect (De Burgh Daly, von Euler, Levin, Hebb, and others). For example, bronchial asthma can be produced also with the stimulation of the sympathetic chain. According to Ferenc Kiss, the fibers having an antagonist function cannot be localized to certain nerves, but are mixed.

In order to work out a better surgical method, we have reviewed the experiences in the operations performed up to the present time. From them it can be concluded that the success of the operation is proportional to the degree of denervation. After having accomplished radical bilateral denervation (Rienhoff and Gay), lasting good results—eight years—have been observed. According to the data in the literature, if only the vagus nerve or the sympathetic denervation is completed, the remaining system is still able to maintain asthmatic conditions. These experiences can be understood from the described anatomic and physiologic conditions.

Considering these aspects, it seemed logical to perform an intervention which extended to both sides equally and which involved, in one intrathoracic operation, the interruption of the pulmonary branches of the vagus—from the recurrent nerve to the pulmonary ligament (Klassen, Clark)—and the removal of the lung's main sympathetic control transmitted by the ganglia of the second to fifth thoracic vertebrae (Miscall and Rovenstine, Carr and Chandler). Hence, a complete sympathectomy can be produced, and at the same time, the dangerous operations carried out in the hilus can be avoided, although the results are good (Rienhoff and Gay, Blades and his co-workers). These authors, besides transecting the pulmonary plexus, denude the main bronchi and the great pulmonary arteries and veins to attain a complete sympathetic denervation.

3. Prior to the application to the vegetative nervous system of the operation based on the knowledge mentioned above, the question arose, will any damage of the respiratory function follow?

Fontaine and Herrmann proved with experiments on animals that, after the transection of the pulmonary branches of the vagus nerve and the upper thoracic sympathectomy, the function of respiration and circulation did not change, and no kind of defect and damage could be observed. The studies of bilateral radical intervention on man prove, also, that after the operation, the respiration, cough, and expectoration are undisturbed. Neurohistologic examinations, after the interruption of the lung's extrinsic vegetative pathways, show a relative automatism to the intrapulmonary (intrinsic) nervous system (Dijsktra, among others). Therefore, after the bilateral denervation of the lung, the remaining part of the neurohormonal regulating system, restoration of a stabilized condition of the thorax, and intact dynamic factors can further ensure—without noticeable defect—the function of the lung and the adaptability of the respiration.

Our Examinations Before the Operation Referring to the Pathomechanism of the Asthmatic Attack and the Expected Result of the Surgical Treatment.—

In patients having intractable bronchial asthma, we have produced attacks before the operation by giving histamine (Figs. 1, *C* and 3, *C*) and have registered the respiratory function with a spirograph. In 8 patients, we have obtained an average of 25 per cent reduction in the vital capacity and a 16 per cent reduction in the pulmonary ventilation rate maximum. These asthmatic signs can be compared with the original asthmatic attack on the basis of the reduced respiratory function as well as the clinical picture (Dzsinich) (Figs. 1, *D* and 3, *D*). In 8 patients, the vital capacity was reduced on an average of 45 per cent and the pulmonary ventilation rate maximum 46 per cent during an attack. We suppose that in these cases, not only the local pharmacologic effect of the histamine appears to function, but the histamine as an initiating stimulus starts the vicious circle leading to attack.

Since both the sympathetic and the vagus nerves participate in the transmitting of the afferent and efferent impulses maintaining the vicious circle, we have attempted the relief of the genuine attack as well as of the attack caused by histamine by the temporary elimination of the conduction of these pathways. We have blocked the vagosympathetic pathway system in the neck and paravertebrally in the upper thoracic section with Novocain (Visnyevszkij). At each place we have injected 20 to 30 c.c. of ½ per cent Novocain. After the blockade, the attacks have ceased (Figs. 1, *E* and 3, *E*). It is therefore possible that the reflex action maintaining the attacks has been interrupted (the vicious circle of Danielopolu). We have been able to demonstrate objectively the relaxation of the attack after the Novocain blockade with a spirographic curve record. Successful, temporary cessation of the asthmatic attack with Novocain blockade has proved the important role of the lung's extrinsic pathways in the asthmatic attack.

We have been able to draw conclusions concerning the degree of the expected success of the operation from the effects of the vagosympathetic blockade used as a test before the intervention. We also gained information about the reversible or irreversible character of the secondary changes accompanying

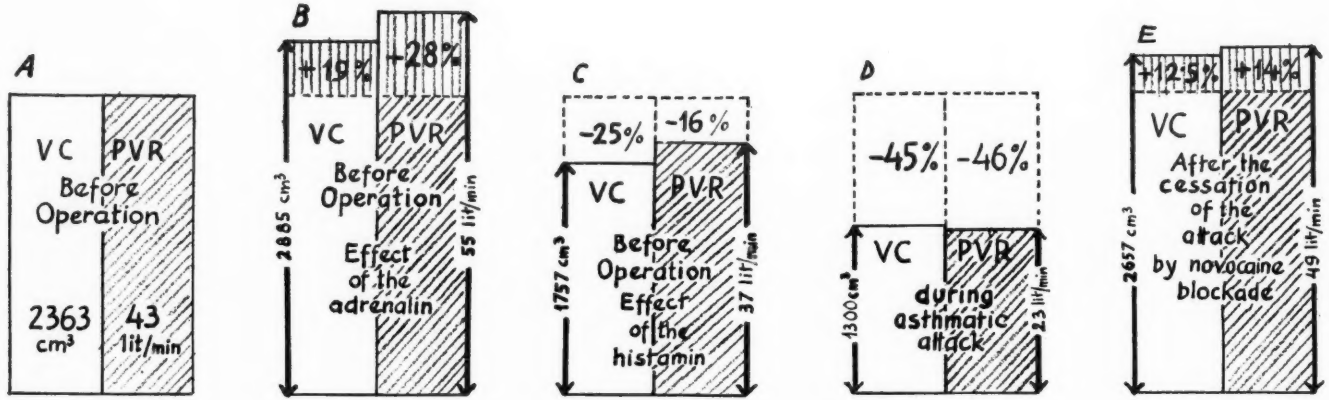


Fig. 1.—The average values of the respiratory function of 8 patients examined before denervation. VC = vital capacity. PVRmax = pulmonary ventilation rate maximum.

the asthmatic condition (emphysema, among others) with a spirographic examination after administering adrenalin to relax the latent bronchial spasm during the period free of attack. (Figs. 1, *A*, *B* and 3, *A*, *B*). (In this period, the vital capacity is 2,363 c.c., the pulmonary ventilation rate maximum is 55 L. per minute. After giving adrenalin, the vital capacity is 2,885 c.c. [an increase of 19 per cent], and the pulmonary ventilation rate maximum is 55 L. per minute [a 28 per cent increase]*). If the attack has ceased after the blockade and the respiratory function values have increased as an effect of the adrenalin given in the period free of attack, we have considered intervention to be justified and assumed that we could expect good results.

Up to the present time we have operated on 30 patients with our surgical procedure, but in this article we are dealing with 19 patients only in summarized evaluation, because we consider in these patients only that the time of observation is sufficient.

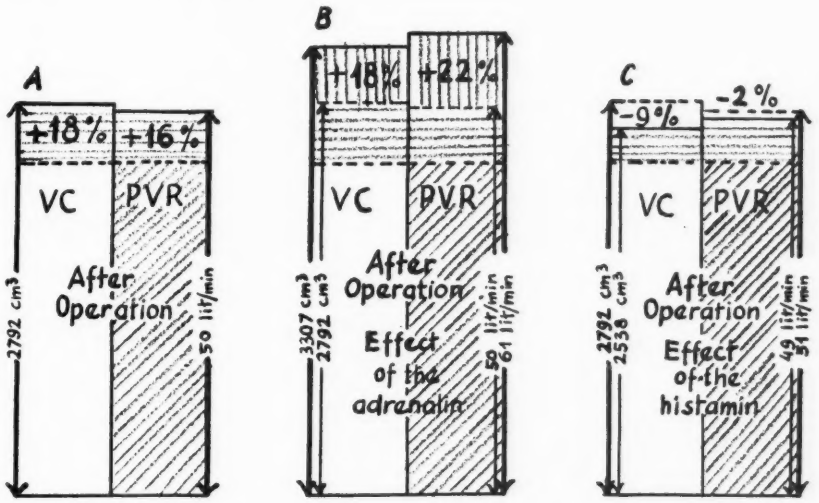


Fig. 2.—The average values of the respiratory function after denervation.

These patients have all suffered from a serious asthmatic status which has resisted various conservative treatments. We want to emphasize from the anamnesis of our 19 patients that 16 of them had some lesion (in most cases infectious) of the respiratory system preceding the development of bronchial asthma, 2 patients suffered damage of the central nervous system (commotio cerebri), and one patient had a psychosis after childbirth. Every one of these coincided with the beginning of the bronchial asthma.

We could not determine the specific stability of the allergens. However, in several cases, due to the occupation of the patients (e.g., druggist, textile

*Average values of the respiratory function.

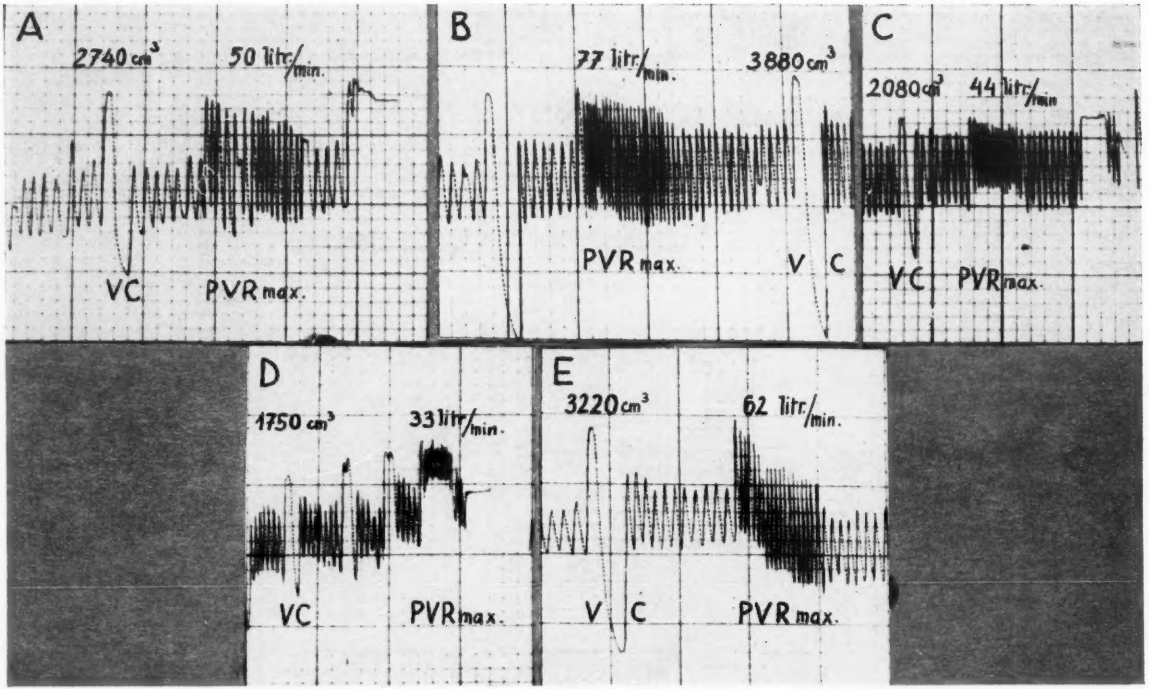


Fig. 3.—The spirographic curves of Patient T. P. before denervation. VC = vital capacity. PVRmax = pulmonary ventilation rate maximum; 1 □ = 200 c.c.

A, In the period free of attack, the respiratory function decreased. The ideal VC for this patient would be 4,480 c.c., the PVRmax would be 72 L./min.

B, The effect of 2 mg. of adrenalin given in the period free of attack. The VC and the PVRmax were considerably increased. The expiration was especially improved.

C, After giving 0.5 mg. histamine, the respiration became dyspneic and the frequency increased. Owing to the reduction of the VC and the PVRmax, it resembles the curve taken during the attack.

D, The curve taken during the asthmatic attack is characteristic; little reserve air, during the definition of the PVRmax the patient ventilates with complementer air.

E, After the bilateral vagosympathetic blockade carried out during the attack, the VC and the PVRmax greatly increased above the values found in the period free of attack.

creased above the values found in the period free of attack.

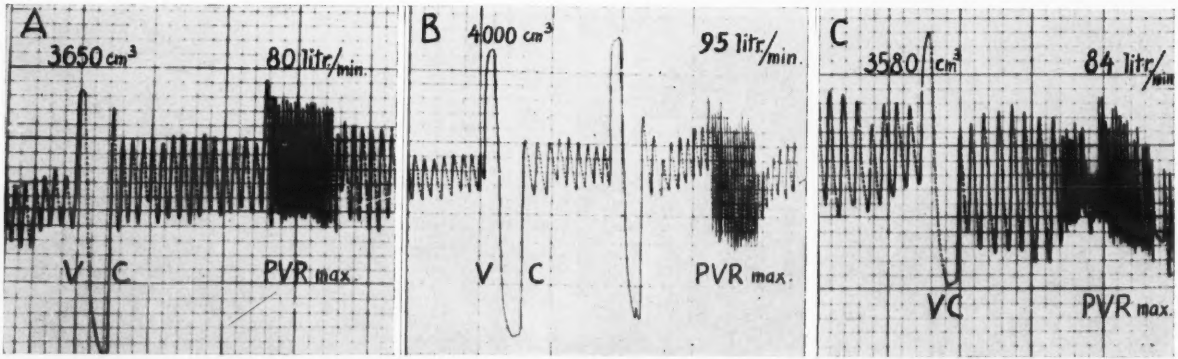


Fig. 4.—Spirographic curves taken three months after the bilateral denervation. *A*, Marked increase in the VC and PVR-max after operation; reserve air increased. *B*, After giving 2 mg. of adrenalin, the VC and PVRmax show the highest value among all other curves (increased adrenalin sensitivity). *C*, After giving 0.5 mg. histamine, the respiratory function did not change considerably (paroxysmal syndrome did not appear).

and leatherworker) a possible sensitivity to certain materials could be assumed. A large number of the patients had previously gone through various nonspecific desensitivity processes without success.

Of the 19 patients, there were 12 men and 7 women. Their ages were between 19 and 55, most of them were between 40 and 50 years of age. The period of their illness was between 5 and 20 years; most of our patients had suffered from asthma for more than 10 years.

The examination of our patients covered particularly the condition of the cardiorespiratory system. We considered as contraindications to surgical treatment only those conditions, which would prevent a major surgical operation (decompensation, among others).

In preparation for intervention, we considered it important to assure a period free of attack, and instituted the removal of the bronchial secretion, adequate treatment of the infectious processes with antibiotics, oxygenization, cardiac reinforcement, and other measures.

*The Essential Part of the Surgical Technique**.—Bilateral intrathoracic intervention (in the fourth intercostal space on the right side, and in the fifth intercostal space on the left side) is made with a parascapular incision, using local anesthesia. After opening the mediastinal pleura, we resect the branches of the vagus nerve going to the lung from the recurrent nerve to the pulmonary ligament. Lifting out the vagus trunk from the mediastinum, we suture the mediastinal pleura underneath in order to prevent regeneration. After the opening of the parietal pleura, we remove the sympathetic ganglion chain of the second to fifth thoracic vertebrae by the transection of the rami communicantes. We tested starting the denervation first on the right, then on the left side, but realized that the order of succession did not make any difference. We performed the contralateral operation after the complete postoperative restitution following the first operation.

We have accomplished bilateral lung denervation in 12 patients, and unilateral lung denervation in 7 patients. There was one death directly after the second intervention during the bronchoscopic aspiration. One of our patients died 9 months after the unilateral denervation with bilateral pneumonia complicated with epidemic influenza. According to the postoperative symptoms, this death could not have been due to the operation.

Surgical Complications.—The most critical was a 3-minute cardiorespiratory syncope following intrathoracic Novocain blockade of the vagus trunk which we have discontinued, using the ordinary methods of resuscitation. Technical errors due to inexperience have caused the only recurrent nerve paresis observed and, in one case, a temporary atony of the stomach followed strong stretching of the vagus nerve. In 2 cases we have observed a Horner syndrome lasting for a few months. A spontaneous pneumothorax occurred in one case in the postoperative period that was associated with the great emphysema of the asthmatic patients.

*Detailed description in J. Internat. de Chir. Bruxelles, 13: 588, 1953.

The success of our surgical treatment has been evaluated on the results of the data of the objective examinations, and of the changes noted in the condition of the patients.

Results of the Objective Examinations.—

Changes in the respiratory system: We have determined with bronchoscopic examination that the changes in the mucous membrane have regressed. The mucous membrane was swollen, mucilaginous, or inflamed before operation in 12 patients. Findings in 5 of these patients became negative after operation. In 5 patients, the changes of the mucous membrane have been relieved. In one patient who has had only unilateral denervation so far, no change has followed. Parallel with the changes of the mucous membrane, expectoration has ceased or decreased. Before operation, 11 patients had a large quantity of sputum. After operation, in 8 of them the production has practically discontinued. There has been a decrease in 2, and an increase in one. The purulent character of the sputum in 6 patients has disappeared. In 2 of these cases, we have performed lobectomy because of bronchiectasis. In the sputum of 15 patients, we have found eosinophils. After operation, this eosinophilia has disappeared in 12 patients; in the other 3, it has decreased. Thus, we have established that on the operated side the allergic and infectious processes of the bronchial system have either stopped or been relieved.

With physical examination, it has became manifest that after the surgical treatment a favorable change has occurred in the inspiratory position of the lung, if rigidity of the thorax has not developed up to this time. The characteristic asthmatic auscultatory signs have ceased or considerably decreased depending on whether uni- or bilateral denervation was performed, that is, what was the degree of reversibility of the changes before the operation?

Radiographic morphologic examination: We have showed that after the denervation there is improvement or normalization of the secondary changes accompanying the asthmatic condition, especially as demonstrated by indirect signs of improvement of emphysema (in the horizontal position of the ribs, in the deep position of the diaphragm). (Fig. 5). Among the 11 bilaterally denervated patients, improvement was observed in 7 cases; among the 7 unilaterally denervated patients, 3 have improved. The character of the emphysema in these patients has been reversible and functional up to now. In 3 patients, among the bilaterally denervated, the changes have been irreversible. In one case, however, we have not observed any improvement, owing to the surgical complication of recurrent nerve paresis.

It has been well demonstrated by bronchograms that the increased tone of the bronchi, compared with the picture before the intervention, shows that the diffuse spastic condition has disappeared or been reduced according to whether the operation has been done uni- or bilaterally (Fig. 6). Relaxation in the spastic condition of the bronchi on the operated side could be observed even after the unilateral denervation. In 4 cases, we have showed the destructive changes of the bronchi before the surgical treatment: bronchiectasis

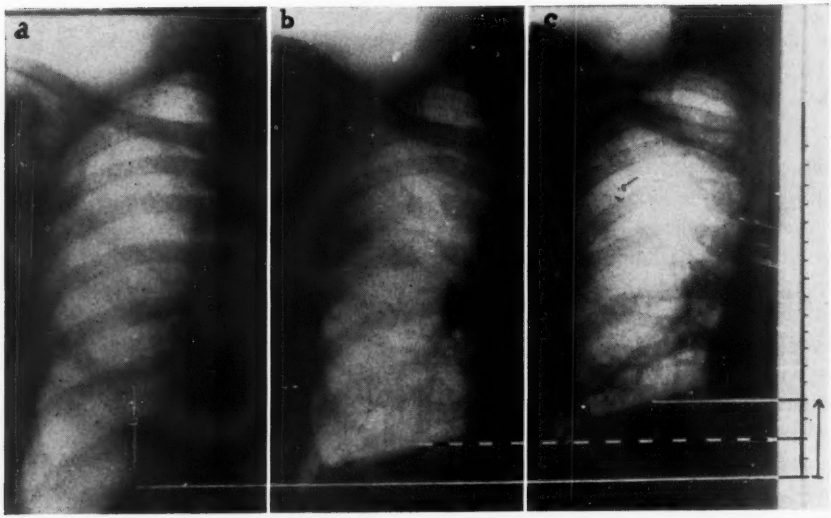


Fig. 5.—X-rays taken from the right side of the thorax of K. L. which show the changes that occurred in the position of the diaphragm. *a*, The right diaphragm stands in the level of the eleventh rib before denervation. *b*, One month after denervation the right diaphragm stands a little under the tenth rib. *c*, Fourteen months after denervation the right diaphragm stands in the line of the tenth rib.

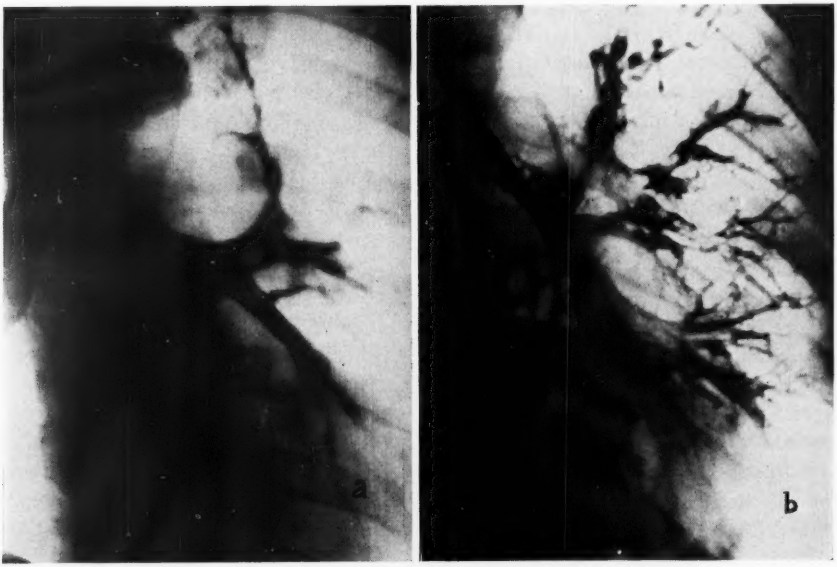


Fig. 6.—A comparison of the bronchograms of T. P. taken before and after the denervation; *a*, spastic condition in the whole bronchial system before denervation. In spite of the pressure of the opaque medium, the peripheral bronchi did not fill up. *b*, After denervation the spastic signs disappeared and the peripheral branches easily filled up. To a certain extent, alveolar filling can also be observed.

in 2 cases when we have performed lobectomy at the same time as denervation, and deforming bronchitis in the other 2 cases, which remained unchanged after the operation.

On examining the function of the bronchi of asthmatic patients by means of bronchography, we have found that after denervation the bronchi approached a normal condition during coughing except in instances of a deforming bronchitis.

Examination of the respiratory function: Owing to the constant bronchial spasm and the reversible or irreversible emphysema existing in the asthmatic condition, the efficiency and the adaptability of the lung in the period free of attack is changed also. We have determined the reduced respiratory function before the operation and the improvement after the operation by means of objective measurements (Fig. 2, *A* and 4, *A*). In 18 patients, the average value of the vital capacity before the operation was 2,363 c.c. in the period free of attack. The average value after the intervention was 2,792 c.c., hence the average rise was 18 per cent. There was an average increase in 10 cases of 20.4 per cent, no change in 2 cases, and a decrease in 6 cases. This decrease did not exceed the degree of reduction in the respiratory function that accompanies thoracotomy. Causes of the reduced vital capacity are: irreversible emphysema, silicosis, deformity of the thorax, pectus carinatum, lobectomy, emphysema after postoperative spontaneous pneumothorax.

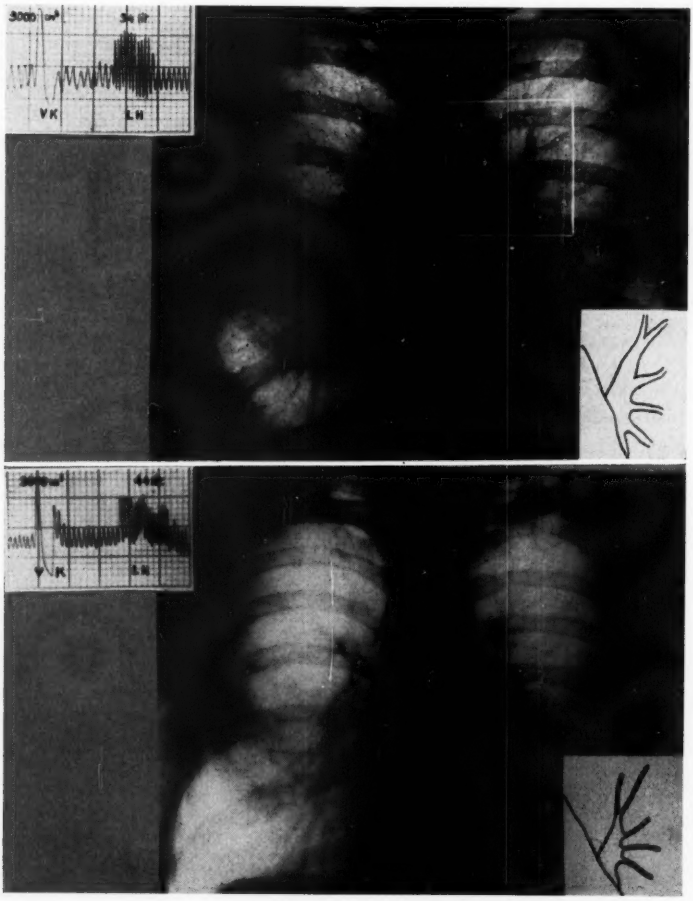
Before operation, the average pulmonary ventilation rate maximum of 8 patients was 43 L. per minute. Postoperatively, the average value rose to 50 L. per minute, which meant a rise of 16 per cent. There was an increase in 2 cases, no change in one case, and a reduction in 2 cases. In the latter 2 cases, lobectomy was performed.

Concerning the question of damage, we can point out that after a systematic follow-up of the patients' condition, we have not been able to observe any sign in the postoperative period that indicated any reduction of the defensive ability of the respiratory function and the lung.

Summary of examinations: Our examinations on the respiratory system show that the interruption of the extrinsic vegetative innervation of the asthmatic lung can be brought into relation with the cessation or the improvement of the allergic and infectious processes of the lung, on the one hand, and the spastic condition of the bronchial system, on the other hand. Parallel with the relaxation in the asthmatic bronchial spasm, the secondary changes—but, first of all, the morphologic signs of reversible emphysema—have improved, in some cases, almost entirely regressed. Changes which already have become irreversible, such as substantial emphysema and rigid thorax, have not changed essentially. According to bronchograms taken during coughing, the function of expectoration of the bronchial system has not exhibited any damage; on the contrary, it has improved considerably.

After the denervation, the relaxation of the bronchial spasm and the improvement of the secondary but reversible emphysema were followed by a favorable change of the respiratory function which was expressed in higher vital capacity and pulmonary ventilation rate maximum.

A.



B.

Fig. 7.—Comparison of the x-rays of the thorax and the spirographic curves of E. R. taken before the operation and after left-side denervation. *A*, Preoperative. *B*, Postoperative.

The outlines of the pulmonary blood vessels on the left side around the hilus show a moderate decrease and the trunk and the upper lobe branch of the pulmonary artery seems to be narrower, whereas on the nonoperated side it is unchanged. The improvement of the respiratory function is expressed in higher pulmonary ventilation rate maximum.

Owing to the functional unity of the cardiovascular and the respiratory system, we have extended our examinations to the circulatory system. Our

physical, radiographic, and electrocardiogram examinations have justified our suppositions that the denervation of the lung in asthmatic patients has not exerted any harmful effect on the circulatory system and on the circulation itself, but it might bring improvement in the circulatory disturbances associated with an asthmatic condition (Figs. 7 and 8).

The clinical symptoms induced by the venous stasis and the change of configuration of the heart have regressed.

The electrical axis deviation owing to hypertension of the pulmonary blood circulation and the signs in the electrocardiogram of the relative myocardial ischemia, following strain of the circulation, have shown regression. We have not seen any substantial change in the pulse and the blood pressure after denervation.

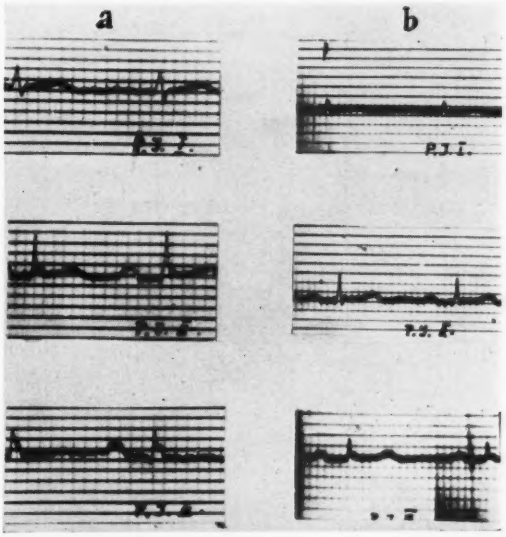


Fig. 8.—Electrocardiogram curves of P. J. *a*, Before the operation, 96-frequency sino-rhythm. P_2 and P_3 are higher and wider (P_2:0.10 sec.; P_3:0.10 sec.). T wave is depressed in Leads I and II and it is in the isoelectric line in Lead III. *b*, After the operation. 60-frequency sino-rhythm. P_2 and P_3 became lower, their width did not change. The T wave became higher in Lead II, and in Lead III a positive T wave can be seen.

Comparison: After the operation the T waves became normal and the somewhat wider P_2 and P_3 waves became lower.

Our later observations with clinical, radiographic, and electrocardiographic examinations did not show any signs of increased use of the right side of the heart, pulmonary hypertension, or stasis of the pulmonary blood circulation.

Owing to the part played by the nervous system in bronchial asthma and to the neurosurgical character of the intervention, we have noted the neuropsychiatric status of every patient before and after operation.

A significant decrease of eosinophilia must be mentioned (Fig. 9). The results of the laboratory examinations (blood count, basal metabolism rate,

liver function test, serum electrolyte, among others) after the operation also support our conclusion that the denervation is not followed by any damage to the general condition of the organs.

The Changes Produced in the Condition of the Patients.—The most important result of the operation was that the heavy and frequent attacks accompanied by the asthmatic condition have been stopped or considerably reduced depending on the extension of denervation (uni- or bilateral), and the degree of reversibility of the secondary changes.

Considering the subjective data, the ability to work, and the findings of the objective examinations just described, we have divided the patients into three groups based on the result of the treatment.

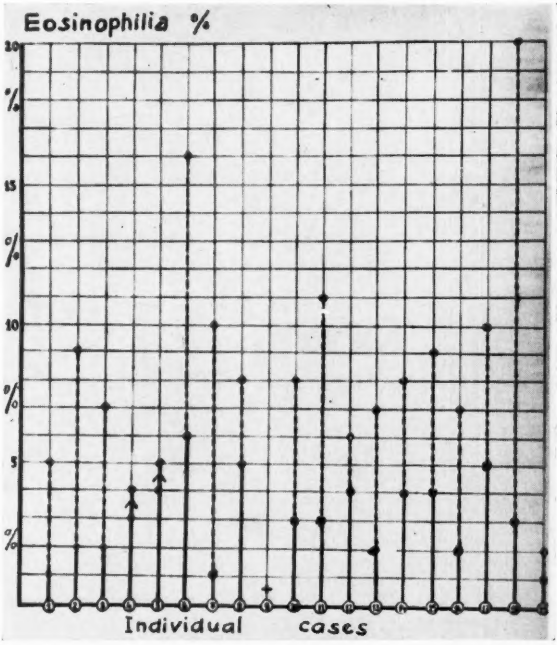


Fig. 9.—The development of the blood eosinophilia in our denervated patients. The values before the denervation are marked with a circle, after the denervation with a dot.

1. In the first group were those patients whose frequent attacks accompanied by the asthmatic condition have ceased to recur. They can continue their occupation and practically do not need any further treatment. Of 19 patients, 10 belonged to the first category. With the exception of 2 patients, they all had bilateral denervation. In this group besides the denervation, 2 patients also had lobectomy performed because of bronchiectasis.

2. In the second group were those patients in whom dyspnea or less severe asthmatic attacks, which could be easily controlled by drugs, sometimes

occurred. In these cases we could not recognize an asthmatic condition postoperatively. These patients were also able to return to employment but only in an easier sphere of work. Seven patients belonged in this category. In 2 of them bilateral and, in the other 5, unilateral denervation was performed. It should be noted that in the 2 bilaterally denervated patients irreversible changes have existed previously. Because of the bisystemic and bilateral innervation of the lungs, final results cannot be determined after unilateral interventions. Therefore, evaluation is only possible after the second operation.

3. In the third category, we listed our only patient who did not improve. In this case, a recurrent nerve paresis (right side) occurred as a surgical complication. Although bilateral denervation was performed, improvement could not be observed.

The time of follow-up extends from the first intervention to one to three years. That involves six seasons of the year in which the asthmatic condition usually becomes worse. The time of follow-up points out the lasting efficacy of the operation.

Concerning the selection of time for surgical intervention, our opinion is that it is advisable to perform the operation before the secondary changes become irreversible, because in this manner, besides the disappearance of the heavy and frequent attacks accompanying the asthmatic condition, the secondary changes also regress.

Explanation of the Mechanism of Action of Denervation and Conclusions.— The therapeutic effect of the intervention can be explained with the bilateral elimination of the extrinsic vagus and sympathetic pathways of the lung. Our surgical procedure interrupts more radically and therefore more efficiently the direct neural afferent and efferent connection between the vegetative centers and the lung. Thus, the vicious circle of the reflex actions, playing an important part in the production of attacks, can be abolished or greatly reduced in its intensity.

We have carried out examinations of the respiratory function after denervation in order to clarify the effect of the intervention.

Before operation, the humoral stimulus caused by histamine has been able to provoke attacks. After denervation, under the effect of histamine, we have not observed clinical signs of asthma (Figs. 2, *C* and 4, *C*). Even the reduction in the values of the increased respiratory function characteristic of the attack has not occurred; the vital capacity has been reduced only 2 per cent and the pulmonary ventilation rate maximum in 9 per cent.

We have been able to register the surprising continuous increase of the already well-improved respiratory function under the effect of adrenalin (Figs. 2, *B* and 4, *B*). The vital capacity and the pulmonary ventilation rate maximum have shown a further 18 per cent and 22 per cent rise, respectively. The question arises as to how to interpret the favorable change in the allergic and infectious processes of the lung and in the asthmatic signs and, also, how to explain the unsuccessful use of histamine and, at the same time, the better adrenalin effect after the denervation.

It is well known that during the allergic and infectious processes, histamine-like materials ("H" materials: acetylcholine, histamine) have been released. These chemical mediators, as we have already stated, play an important role in the pathomechanism of the asthmatic attack.

On the basis of our observations and the data from the literature, our opinion is that the denervated asthmatic lung* reacts as if it were "more resistant" in relation to parasympathomimetic mediators producing the allergic and infectious processes or other stimuli. These chemical materials—besides the local temporary effect—were not able to produce the vicious circle of the reflex actions needed for the asthmatic paroxysm since we had interrupted the vagosympathetic pathways conducting the pathologic reflexes between the vegetative centers and the lung. The regression of the allergic and infectious processes of the lung, the normalization of its tendency to allergy and infections, and of its pathologically increased reactivity may be due to the elimination of the reflex action. The favorable change in reactivity can be further attributed to better adrenalin effect proved by us. Co-Tui has shown, with experiments in animals, that after the denervation of the lung, the bronchioles also become sensitive to adrenalin in their own circulation, in the same manner as the blood vessels. Our studies confirm the idea of an increased adrenalin sensitivity of the denervated human lung.

Finally, the chemical mediators released during the allergic and infectious processes developed after the denervation are not able to start reflex actions producing a paroxysmal syndrome. At the same time, by means of the increased adrenalin sensitivity of the pulmonary tissue, the antagonism to the physiologic quantity of adrenalin circulating in the blood is able to compensate for the local effects of these materials, which are manifest in parasympathetic signs (bronchial spasm, hypersecretion, and so forth).

In physiologic conditions, the alternations of the antagonist parasympathetic and sympathetic effects are in equilibrium. The wide scale of stimuli in the asthmatic lung can upset the equilibrium and produce a pathophysiologically increased parasympathetic effect responsible for the asthmatic condition. After the most radical elimination of the extrinsic innervation of the lung, the state of equilibrium becomes stabilized.

Furthermore, we came to the conclusion that in the asthmatic status, the conduction of the direct vagosympathetic pathway connecting the vegetative center with the lung means a harmful rather than beneficial function for the organism. Since it conducts the reflex actions leading to attack, its function changes from physiologic to pathologic. Thus, the well-known secondary changes (emphysema, strain of the circulation, among others) become worse and irreversible. In this case, we consider the elimination of the extrinsic pathways to be justified. Then it is even more beneficial because the function of the lung and the adaptability of the respiration are not exposed to damage. Our suppositions have been greatly supported by the practical observation that

*We are applying the expression of lung denervation for denoting the character of the intervention. Anatomically and physiologically the organs could not be entirely denervated.

the biologic capacity and adaptability of our asthmatic patients have not declined; on the contrary, they have improved considerably during many years of observation.

SUMMARY

In the pathomechanism of the asthmatic attack, we attach great importance to the reflex actions maintaining a vicious circle, transmitted between the vegetative centers and the lung by the lung's extrinsic vegetative pathways.

In cases of intractable bronchial asthma, because of the bilateral and bisystematic innervation of the lung, we have used a surgical intervention in which the afferent and efferent innervation of the lungs on both sides has been very radically interrupted (the pulmonary branches of the vagus nerve and the sympathetic ganglia of the second to fifth thoracic vertebrae have been resected).

As regards the efficiency of the operation, the results obtained as compared with the test examinations before the operation are as follows:

Of the 19 patients operated on, the results were very good in 10; and good in 7. One patient has remained unchanged. Soon after the second intervention, one patient died.

Objective examinations have demonstrated that after the intervention, the allergic and infectious processes of the lung have regressed, the spastic condition of the bronchi has relaxed and, along with these, the reversible secondary asthmatic changes have improved. We have not observed any damage.

During the time of observation, up to three and one-half years, no regression of the good results has been observed.

The favorable effect of the operation is attributed to the stabilization of the vagosympathetic equilibrium in the asthmatic lung, isolated from the vicious circle of pathogenic reflex actions. We demonstrated the resistance of the lung to "H" materials, on the one hand, and increased adrenalin sensitivity, on the other. Parallel with these results, a favorable change occurs in the reactivity of the lung, that is, it becomes normal.

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PULMONARY CYSTIC DISEASE: PHYSIOLOGIC STUDIES AND RESULTS OF RESECTION

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INTRODUCTION

IT IS among the purposes of this paper to show that resection of large pulmonary cysts in selected patients is followed by striking improvement in respiration. This favorable effect may be particularly evident in patients for whom hypoxia is one of the manifestations of impaired lung function. These results of surgery stand in contrast to those previously reported[1] in patients for whom hypoxia was interpreted to be among the contraindications to resection.

There have been relatively few published studies of the functional consequences of treating pulmonary air cysts by resection. Three articles dealing primarily with the physiology of cystic disease have appeared in the American literature.[1-3] Of the patients included in these, 5 were treated surgically; 2 by pneumonectomy, and 3 by subtotal resection.[1, 2] The scarcity of the data which came to our attention prompted a review of the pulmonary function studies of 11 men with unilateral and bilateral cystic disease. Six patients, of whom 3 were studied before and after resectional therapy, were selected as representative of the group.

Some patterns of physiologic abnormality into which these patients were placed are among those described by Baldwin and her colleagues[1]: (1) those with free bronchial communication and normal lungs, and (2) those with poor or intermittent bronchial communication and normal lungs. In addition to these recognized functional types, we have included patients in whom cystic disease was associated with poor oxygenation of arterial blood and who did

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TABLE I. PRE- AND POSTOPERATIVE VOLUMETRIC AND VENTILATORY

CLINICAL DATA					LUNG					
					V.C.				R.V.	
PATIENT NO.	AGE (YRS.)	B.S.A. M^2	MONTHS POSTOP.	SIDE OF CYST OR OPERATION	C.C.	% OF PRED.	RT. (%)	LT. (%)	C.C.	% OF PRED.
1	29	1.91		Lt.	6403	143	49	51	1547	139
2	25	1.66		Lt.	4149	96	53	47	1551	143
3	27	1.96		Rt.	4644	101	51	49	2588	225
4	49	1.66		Rt.	2480	68			1546	139
			2½	Rt.	3270	90			1205	108
5	43	1.84		Bilat.	4026	99	*	*	2295	185
			3¾	Lt.	3115	77	65	35	1421	115
			3¾	Rt.	2738	67	43	57	1383	112
6	31	1.80		Bilat.	1876	45	38	62	1091	104
			1⅓	Rt.	2466	59			1458	138
			2½	Lt.	2936	70	54	46	1323	126

*Patient unable to perform vital capacity during bronchospirometry.

not suffer from advanced pulmonary emphysema. These are to be distinguished from a group of patients identified by Baldwin[1] in whom the abnormalities of cystic disease were compounded by advanced emphysema.

Cystic disease of the lung is rivaled by few pulmonary lesions in producing a variety of respiratory abnormalities. The number of patients included in this paper was restricted in order to permit discussion of each study individually. The tabular data are supplemented by graphs permitting ready recognition of changes and departures from normal. One of the objectives of this study was, therefore, to illustrate the application and interpretation of function data.

MATERIAL AND METHODS

Clinical data pertaining to the 6 male patients are included in Table I.

The pulmonary function was studied using conventional methods. The maximum breathing capacity, performed in the sitting position, was measured by collecting expired air in a Douglas bag and passing the contents through a gas meter. The best of three fifteen-second attempts was recorded. The subdivisions of the vital capacity were inscribed during closed-circuit spirometry. The timed vital capacity was obtained by measuring the proportion of the vital capacity delivered in one, two, and three seconds of forceful expiration. The functional residual capacity was measured by a modification of the Darling open-circuit method,[4] the figures recorded being the mean of two analyses which checked within 10 per cent. The residual volume was calculated by subtracting the expiratory reserve from this mean value. The alveolar index, the concentration of nitrogen in "alveolar air" after the patient has breathed 100 per cent oxygen for seven minutes, was also measured in duplicate, the mean of the two values appearing in the table.

Bronchospirometry was performed through a Carlens' catheter after topical anesthesia of pharynx, larynx, and trachea with 1 per cent Pontocaine. The total capacity of each lung individually was measured using Darling circuits adapted for simultaneous unilateral determinations.[5] All of the lung volumes were converted to body temperature, ambient pressure, and saturation with water vapor (BTPS).

Blood gas contents and the concentration of nitrogen in air samples were measured using the method of Van Slyke and Neill.[6] Blood gas tensions were measured by the method of Riley.[7, 8] The composition of expired gases was determined with the Scholander apparatus.[9]

DATA IN SIX MEN WITH CYSTIC DISEASE OF THE LUNG

VOLUMES					INTRA-PULMONARY MIXING	VENTILATION								OXYGEN UPTAKE	
T.L.C.		F.R.C.	R.V./ T.L.C. (%)	F.R.C./ T.L.C. (%)		M.B.C.		TIMED V.C. PER CENT			AT REST			
C.C.	% OF PRED.	C.C.			VOLS. % N_2	L./ MIN.	% OF PRED.	1 SEC.	2 SEC.	3 SEC.	RT. (%)	LT. (%)	RT. (%)	LT. (%)
7950	142	3932	19	49	6.29	159	117	86	100	100	48	52	54	46
5700	105	2718	27	48	4.08	121	99	68	80	85	62	38	65	35
7232	126	3738	36	52	4.94	128	90	54	65	73	48	52	8	92
4026	85	1997	38	50	1.43	56	55	50	65	70				
4475	94	1906	27	43	0.69	67	66	66	78	88				
6321	119	3042	36	48	0.75	109	92	62	78	85	56	44	65	35
4536	86	2062	31	45	2.47	82	69	58	76	79	60	40	67	33
4121	78	1982	34	48	0.69	132	112	84	92	100	47	53	43	57
2967	56	1091	37	37	2.76	80	63	79	90	94	39	61	38	62
3924	75	2035	37	52	2.75	136	107	85	89	93				
4259	81	1950	31	46	0.72	108	85				60	40	57	43

The methods of Lilienthal and co-workers,[10] and Riley and his colleagues[11, 12] were used in measuring the pulmonary diffusing capacity[13] and the ventilation-perfusion relationships. The latter term refers to the *distribution* of blood and gas within the lungs and is expressed in terms of physiologic dead space (V^c_D/V_T) and venous admixture ($\dot{Q}_{va}/\dot{Q}_t$). A high dead space (exceeding 30 per cent of the tidal volume) indicates that an unusually large proportion of air entering the respiratory tract is distributed to nonperfused or poorly perfused areas. A patient with occlusion of a branch of the pulmonary artery would have an elevated dead space. The measurement is based on the assumption that expired air can be considered to be made up of two fractions, one having the carbon dioxide content of inspired air and originating in dead space and the other having the carbon dioxide content of alveolar gas. The dead space ratio indicates the proportions of these two gases which, if mixed, would result in gas with the composition of expired air.

The venous admixture ratio is similar in concept. One assumes that peripheral arterial blood is a mixture of two streams, one being mixed venous blood and the other blood in equilibrium with alveolar air. In normal individuals, the saturation of arterial blood is equal to that of a mixture containing 6 parts or less of mixed venous blood and 94 parts or more of blood in equilibrium with alveolar gas. Venous admixture ratios in excess of 6 per cent indicate that an unusually large proportion of the right cardiac output is distributed to unventilated or poorly ventilated areas. In calculating the venous admixture ratios of the present patients, mixed venous blood was assumed to be 25 per cent less saturated than pulmonary capillary blood when the patient was at rest and 40 per cent less saturated during treadmill exercise.

Oxygen diffuses from alveolar gas into pulmonary capillary blood because the pressure of oxygen in the alveolus ($P_{A_{O_2}}$) exceeds that in the pulmonary capillary ($P_{C_{O_2}}$). The diffusing capacity of the lung is the volume of oxygen ($\dot{V}_{O_2}$) which diffuses across the alveolar-capillary membrane every minute per unit of pressure difference between the two sides of this membrane. It is calculated by dividing the oxygen uptake ($\dot{V}_{O_2}$) by a mean value for the pressure difference in mm. Hg between the two sides of this membrane ($\overline{P_{A_{O_2}}-P_{C_{O_2}}}$). It is low either when the dimensions of the alveolar-capillary bed have been reduced, as after pulmonary resection,[14] or/and when the membrane becomes less permeable to oxygen, as in the granulomatous diseases.[15] In the absence of the latter, it is an index of the size of the alveolar-capillary bed and is interpreted as such in this paper.

When one exercises, the diffusing capacity increases, reaching a maximum value when the oxygen uptake approaches 1,200 c.c. per minute. Under these circumstances the dimensions of the alveolar-capillary bed approximate their maximum value. The maximum diffusing capacities of 9 young men with minimal or no demonstrable pulmonary pathology studied at the St. Albans laboratory[14] ranged from 68 to 86 with a mean of 76.

TABLE II. PRE- AND POSTOPERATIVE GAS EXCHANGE

					ANALYTICAL				
PATIENT NO.	PRE- OR POSTOP.	ACTIVITY	Sa_{O_2} (%)	Pa_{O_2} (MM. Hg)	Ca_{CO_2} (VOLS. %)	Pa_{CO_2} (MM. Hg)	BP-47 (MM. Hg)	$\dot{V}$ (L./ MIN.)	V_T (C.C.)
1	Pre	Rest	96.1	91	51.41	41	722	8.9	533
		Exercise	96.3	94	43.40	42	722	40.8	1571
		Exercise	78.3	43	37.87	37	722	67.2	
2	Pre	Rest	97.2	91	51.06	41	714	6.7	404
3	Pre	Rest	94.8	83	38.77	35	705	11.0	449
4	Pre	Rest	90.9	70	48.45	45	709	9.2	551
		Exercise	89.2						
	Post	Rest	94.9	83	50.01	43	722	14.2	835
		Exercise	91.1						
5	Pre	Rest	94.8	86	42.96	35	712	8.1	1071
		Exercise	96.1						
	Post I	Rest	93.5	78	43.94	37	707	6.9	691
		Exercise	93.9						
	Post II	Rest	96.6	93	45.72	44	723	8.4	704
		Exercise	93.9						
6	Pre	Rest	92.0	69	46.92	35	717	7.9	265
		Exercise	88.0	58	39.99	28	717	44.0	1190
		Exercise	67.0	34	36.65	29	717	47.8	1290
	Post I	Rest	95.3	83	50.20	44	711	7.1	420
		Exercise	94.9	83	44.47	39	711	42.1	1212
		Exercise	70.3	40	38.17	36	711	49.3	1333
	Post II	Rest	95.3	86	51.18	46	703	6.3	365
		Exercise	94.9	86	42.82	40	703	40.0	1160
		Exercise	66.6	39	34.49	36	703	55.6	1333

The following conventional abbreviations[16] appear in Tables I and II:

B.S.A., M^2—Body surface area in square meters

V.C.—Vital capacity

R.V.—Residual volume

T.L.C.—Total lung capacity

F.R.C.—Functional residual capacity

R.V./T.L.C.—Ratio of the residual volume to the total lung capacity in per cent

F.R.C./T.L.C.—Ratio of the functional residual capacity to the total lung capacity in per cent

M.B.C., L./min.—Maximum breathing capacity in liters per minute, BTPS

$S_{a_{O_2}}$, %—Oxyhemoglobin saturation of arterial blood in per cent

$P_{a_{O_2}}$, mm. Hg—Partial pressure of oxygen in arterial blood in millimeters of mercury

$C_{a_{CO_2}}$, Vols. %—c.c. of carbon dioxide contained in 100 c.c. of arterial blood

$P_{a_{CO_2}}$, mm. Hg—Partial pressure of carbon dioxide in arterial blood in millimeters of mercury

BP-47, mm. Hg—Barometric pressure minus correction for water vapor tension of air saturated at body temperature, in millimeters of mercury

$\dot{V}$, L./min.—Total ventilation in liters per minute, BTPS

V_T, c.c.—Tidal volume in c.c., BTPS

$F_{e_{CO_2}}$, %—Concentration of carbon dioxide in expired air in per cent

R—The gas exchange ratio, or respiratory quotient, i.e., carbon dioxide output divided by the oxygen consumption

DATA IN SIX MEN WITH CYSTIC DISEASE OF THE LUNGS

DATA				DERIVED VALUES					
						DISTRIBUTION		DIFFUSION	
								MAX. DIFF. CAP.	
$F_{E_{CO_2}}$ (%)	$F_{I_{O_2}}$ (%)	R	$\dot{V}_{O_2}$ (C.C./MIN.)	$P_{A_{O_2}}-P_{a_{O_2}}$ (MM. Hg)	$\overline{P_{A_{O_2}}-P_{c_{O_2}}}$ (MM. Hg)	$V^c{}_D/V_T$ (%)	$\dot{Q}_{va}/\dot{Q}_t$ (%)	TOTAL	M^2
3.241	20.93	0.76	315	9		30	4		
4.255	20.93	0.94	1546	12	31	22	3		
3.359	13.15	1.12	1685	19	31		3	54	28
3.523	20.93	0.84	234	11		21	7		
2.762	20.93	0.75	331	22		31	10		
3.284	20.93 20.93	0.85	292	26		36	19		
3.337	20.93 20.93	0.84	471	19		36	10		
3.292	20.93 20.93	0.80	276	21		26	9		
3.352	20.93 20.93	0.77	249	25		26	15		
2.933	20.93 20.93	0.84	247	8		42	3		
2.591	20.93	0.87	197	42		29	24		
3.668	20.93	0.98	1362	63	45	56	26		
2.973	14.26	1.08	1065	41	45	32	26	24	13
2.852	20.93	0.87	193	16		22	8		
3.600	20.93	0.91	1376	23	30	29	7		
3.141	13.44	1.07	1201	22	30	27	7	40	22
3.188	20.93	0.76	214	3		34	2		
3.770	20.93	0.85	1442	16	31	29	6		
3.164	13.05	1.17	1224	22	31	33	6	40	22

$\dot{V}_{O_2}$, c.c./min.—Oxygen uptake in c.c. per minute, STPD

$P_{A_{O_2}}-P_{a_{O_2}}$, mm. Hg—Oxygen partial pressure difference in millimeters of mercury between "alveolar air" and peripheral arterial blood

$\overline{P_{A_{O_2}}-P_{c_{O_2}}}$, mm. Hg—Mean oxygen pressure difference between alveolar air and pulmonary capillary blood

$V^c{}_D/V_T$, %—Ratio of dead space to tidal volume in per cent

$\dot{Q}_{va}/\dot{Q}_t$, %—Ratio of the venous admixture to cardiac output in per cent

Max. Diff. Cap.—The maximum diffusing capacity

PATIENT NUMBER ONE

Clinical Summary.—This 29-year-old white man was admitted for study after pulmonary pathology had been disclosed by routine chest roentgenograms. An infection with histoplasmosis had been established by gastric smear two years previously. He was asymptomatic without cough, dyspnea, chest pain, or hemoptysis.

Physical examination revealed normal resonance and breath sounds throughout the chest. A roentgenogram (Fig. 1*A*) showed infiltrative lesions in the apical and posterior segments of the upper lobe of the right lung. Cystic changes were apparent in the left lung with downward displacement

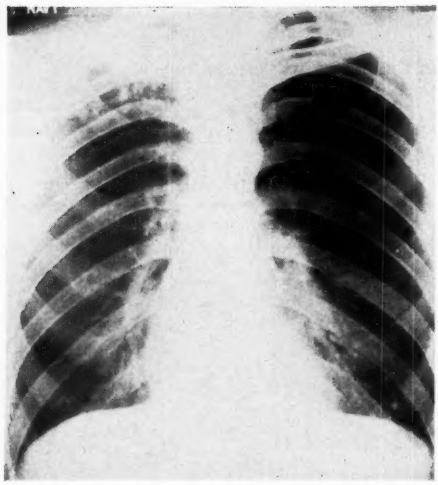


Fig. 1*A*.—Chest roentgenogram. Note infiltrative lesion of right upper lung field and increased radiolucency of left upper hemithorax.

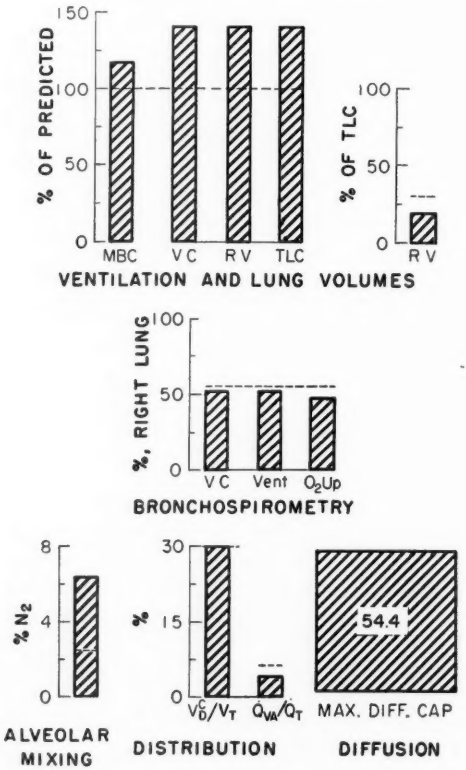


Fig. 1*B*.—Function data of Patient 1. Note absence of large abnormalities except in index of alveolar mixing.

of the hilar markings. Tomograms demonstrated multiple air-containing cysts in the left upper lobe area and compression of the left lower lobe. Pulmonary function studies were obtained (Fig. 1*B*).

During hospitalization he remained well. Since it was the opinion of the medical staff that surgery was not indicated, he was discharged.

Physiologic Studies.—As shown in Tables I and II and in Fig. 1*B*, measurements of the maximum breathing capacity and the lung volumes indicated no abnormality. The studies of unilateral function also failed to reveal noteworthy deficit, for the contribution of the left lung to the vital capacity, ventilation, and oxygen uptake was normal. This normal participation indicated that interference by the cyst and parenchymal infiltrate affected the left and right lungs proportionately. By reducing the performance of the right lung, the infiltrative lesion could well have resulted in increasing to normal limits the relative contribution of the left lung despite some interference with unilateral function attributable to the cyst.

Ventilation-perfusion relationships were also normal as indicated by the dead space (V^c_D/V_T) and venous admixture ($\dot{Q}_{va}/\dot{Q}_t$) ratios. The maximum diffusing capacity was minimally reduced—a finding consistent with decreased permeability of the alveolar-capillary membrane to oxygen and/or with reduced dimensions of the capillary bed in the limited area of infiltration on the right. The nearly normal figure for this measurement, therefore, supports the ventilatory, volumetric, and distribution data in indicating no gross physiologic change attributable to the presence of the cyst.

The index of alveolar mixing was strikingly abnormal (6.296 per cent). In the absence of an elevated residual volume or of an obstructive ventilatory deficit, the most likely explanation for this finding was the presence of a comparatively patent communication between the cyst and the tracheobronchial tree. The incomplete elimination of nitrogen from the cyst during the seven minutes for which the patient breathed virtually pure oxygen was explained by assuming that the tidal exchanges of air between the cyst and the bronchial tree during quiet breathing were small. This explanation was supported by the normal dead space ratio, for this ratio would have been abnormally high had a sizeable structure not participating in gas exchange been well ventilated.

Summary.—This patient was selected for demonstrating that a large air cyst may interfere minimally with tests of respiration. Ventilation, lung volumes, bronchospirometry, ventilation-perfusion relationships, and the maximum diffusing capacity were normal or nearly normal. Only the index of alveolar mixing was patently abnormal.

PATIENT NUMBER TWO

Clinical Summary.—This 26-year-old Negro man was admitted for evaluation of his pulmonary status. Three years previously a routine chest roentgenogram had revealed the presence of a cyst of the left lung in which no change had been detected by yearly studies. He denied cough, dyspnea, orthopnea, hemoptysis, or chest pain.

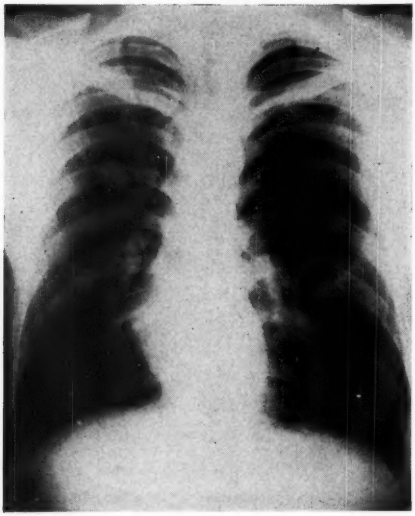


Fig. 2A.—Chest roentgenogram. Note oval radiolucent area in left upper lung field.

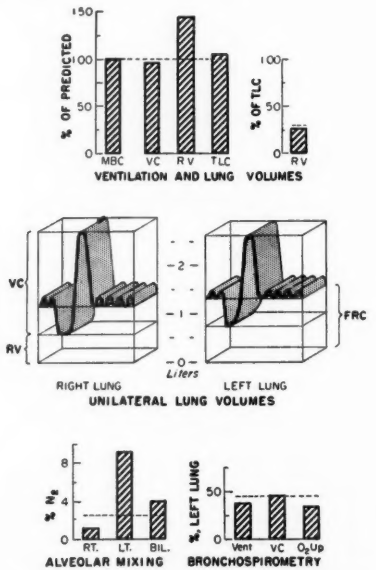


Fig. 2B.—Preoperative function data of Patient 2. The impairment of the left lung is shown by the slope of the expiratory tracing, the elevated residual volume and functional residual capacity, the poor alveolar mixing of respiratory gases, and the diminished contribution to ventilation and oxygen uptake. Maximum breathing capacity and bilateral lung volumes are normal.

On physical examination there were amphoric whispered-voice sounds over the second left intercostal space medial to the anterior axillary line. Chest roentgenograms showed absence of the lung markings in the upper left hemithorax (Fig. 2*A*). The left leaf of the diaphragm was depressed. Pulmonary function studies were obtained (Fig. 2*B*).

On Sept. 14, 1954, a left thoracotomy disclosed emphysematous and cystic changes of the posterior segment of the left upper lobe. The cystic areas were so markedly distended that the remainder of the upper lobe and the superior and posterior basilar segments of the lower lobe were compressed. The cystic and emphysematous areas were removed by wedge excision. Bronchial communications to the upper lobe cyst were demonstrated.

Three months following surgery the patient was returned to full duty.

Physiologic Studies (Fig. 2*B*).—Although the vital capacity was moderately slowed, the maximum breathing capacity was normal. Thus, in spite of evidence for increased resistance to the flow of air during forced expiration, the maximum voluntary ventilation was within the predicted range. Ventilation on the side of the cyst was 38 per cent of the total as compared to a normal of 45 per cent.

The lung volumes were virtually normal. Comparison of the spirometric tracings of each lung (Fig. 2*B*) showed slowing of expiration on the left side during delivery of the expiratory reserve. This unilateral obstruction possibly could be attributed to interference of the bronchospirometric catheter with air flow, to expression of air from the cyst through a narrow communication, to pressure of the cyst on adjacent parenchyma and airways causing trapping in areas distal to the point of compression, or to a combination of these factors. The placement of the catheter appeared to be optimal as judged by fluoroscopy, bronchospirometric tracings, and correspondence between unilateral and bilateral volumetric measurements. The high index of alveolar mixing on the left (9.175 per cent as compared to 1.270 per cent on the right) suggested a communication which was later identified by examination of the resected specimen. Parenchymal compression was demonstrated by roentgenography and confirmed at thoracotomy. It is reasonable therefore to ascribe the prolonged expiration to the effects of the cyst rather than to artifacts of recording.

Obstructive breathing commonly results in elevation of the mid-position. Correspondingly the functional residual capacity and residual volume on the left were higher than on the right side, the opposite of the normal relationship.

The elevation in the bilateral index of alveolar mixing (4.076 per cent) was attributable to mixture in the trachea of gases of unequal nitrogen concentration contributed by the two main-stem bronchi.

The presence of a poorly ventilated cyst complicates determining the functional residual capacity by the Darling technique, for nitrogen elimination from the lungs, which is the basis of the method, is hindered by poor ventilation. It was likely in the present patient that the poor elimination of nitrogen, indicated by the high alveolar index, was not representative of the left lung as a whole but only of the cystic lobe. In order to avoid the errors

introduced by using an artificially elevated value, the mixing index observed for the normal right lung was used in calculating the functional residual capacity of the left lung. This substitution gave a figure 251 c.c. (16.1 per cent) below that obtained by using the high index actually measured. Selection of a figure for the alveolar index was inevitably arbitrary, for there was in fact no index representative of the whole lung but a group of unknown, but widely divergent, indices from pulmonary areas contributing differently to ventilation. By using the index chosen, the sum of the functional residual capacities of the two lungs (2,503 c.c.) fell within 8 per cent of the mean of two bilateral measurements (2,718 c.c.) also computed using a normal index.

Finally, it should be observed that the functional residual capacity and residual volume computed according to these assumptions were minimal figures; although the proportion contributed by the parenchyma was reasonably accurately represented, the volumes of the cysts were underestimated.

Both the physiologic dead space (V^c_D/V_T) and the venous admixture ($\dot{Q}_{va}/\dot{Q}_t$) ratios were normal indicating no gross abnormalities in the relationship between alveolar ventilation and perfusion. Pertinent to this finding was the observation that the oxygen uptake on the left (35 per cent of the total) was reduced in proportion to the reduction in ventilation (38 per cent). Inasmuch as unilateral oxygen uptake is an approximate index of the distribution of blood flow between the two lungs, the proportional reductions in unilateral ventilation and oxygen uptake would be expected in the presence of normal ventilation-perfusion relationships. Two additional inferences were drawn from the fact that ventilation-perfusion relationships were normal: (1) The normal dead space suggested that the cyst (the walls of which were doubtless negligibly perfused) was poorly ventilated. This observation was in agreement with the fact, cited above, that even after the patient had breathed virtually pure oxygen for nine minutes the air contained in the cyst still had a high concentration of nitrogen. (2) The virtually normal alveolar-arterial oxygen partial pressure difference and ratio of venous admixture to total pulmonary flow suggested that the cyst was not compressing unusually large areas of adjacent pulmonary parenchyma.

Summary.—Bronchospirometry was particularly useful in evaluating this patient's respiratory deficit. Slowing of expiration and impaired intrapulmonary mixing of respiratory gases, both of which were demonstrated by the bilateral studies, were shown to be localized to the side of the lesion. There were, in addition, unilateral abnormalities of ventilation, lung volumes, and oxygen uptake not identified by bilateral measurements. The unilateral data were used to illustrate the difficulties of interpreting measurements of the functional residual capacity in the presence of a communicating cyst. Ventilation-perfusion relationships were normal. The preoperative prediction that the cyst was a communicating structure was confirmed at thoracotomy.

PATIENT NUMBER THREE

Clinical Summary.—This 26-year-old Negro male laborer entered the hospital complaining of a nonproductive cough of one year's duration and

progressive exertional dyspnea of three years' duration. There had been two recent episodes of upper respiratory tract infection with fever, chills, and productive cough without hemoptysis. Walking one block or climbing one flight of stairs produced dyspnea.

Physical examination disclosed an essentially symmetrical chest with hyperresonance and decreased breath sounds at the right apex. There were fine inspiratory and expiratory wheezes throughout both lung fields with prolongation of the time required for expiration. There was no cyanosis, clubbing, or edema of the extremities.

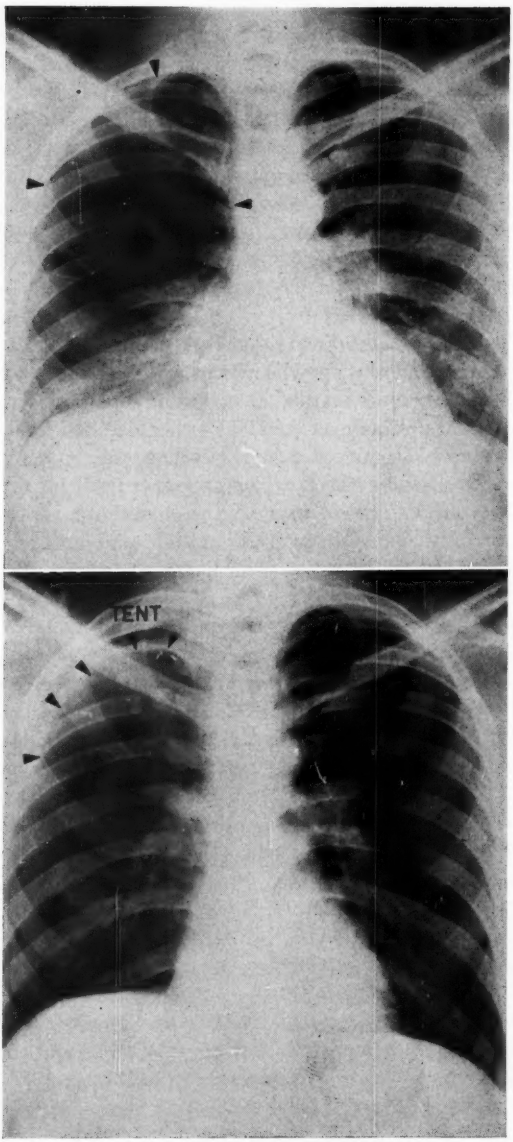
A roentgenogram of the chest outlined a "large area of emphysema bounded by fine linear densities in the right upper lung field extending from the apex to the level of the hilum" (Fig. 3*A*). Pulmonary function studies were obtained (Fig. 3*C*).

On Aug. 5, 1954, a right thoracotomy exposed a large 20 by 15 cm. air-containing cyst occupying the apical and posterior segments of the upper lobe of the right lung. There was marked compression and partial atelectasis of the lower and middle lobes. The cyst could be easily deflated and inflated, demonstrating free bronchial communication. Because of numerous small bullae present along the margin of the anterior segment, the cyst was removed by a right upper lobectomy. The volume of the hemithorax was tailored to the volume and shape of the remaining right middle and lower lobes by creating a new roof (pleural tent)[17] for the pleural cavity from a stripped portion of the cupola.

Three months following surgery, the patient had noted marked improvement of dyspnea.

Physiologic Studies.—The most striking abnormalities presented in Fig. 3*C* are a high residual volume, poor alveolar mixing of respiratory gases, and impaired ability to expire forcefully and rapidly (timed vital capacity). These could all be accounted for by assuming that the cyst communicated poorly, or that it obstructed ventilation of ipsilateral parenchyma, or that generalized emphysema existed. A postoperative study would have differentiated among these possibilities; such, however, could not be obtained. The relatively good maximum breathing capacity did not suggest widespread generalized emphysema. There were, however, indications that the cyst was ventilated and that the function of ipsilateral parenchyma was compromised. At bronchospirometry, the contribution of the right lung to ventilation was found to be better than to oxygen uptake, showing that considerable unperfused, presumably cystic, tissue was being ventilated. Correspondingly, the dead space ratio (V^c_D/V_T) was elevated, though minimally so. The poor contribution to oxygen uptake suggested severely restricted right pulmonary flow, the normal saturation of arterial blood indicating that this flow was distributed for the most part to well-ventilated alveoli. The relative hypoventilation of some perfused areas, however, was shown by the moderately elevated venous admixture ratio (Q_{va}/Q_t). Together with bronchospirometry, therefore, studies of distribution were compatible with ventilation of cysts and restriction of gas exchange in ipsilateral parenchyma.

A.



B.

Fig. 3.—*A*, Chest roentgenogram. Note radiolucent area in right upper lung field and density in right lower lung field.

B, Chest roentgenogram five weeks following excision of right lung cyst and construction of pleural tent.

In addition, there was hyperventilation. Shortness of breath had been among the patient's complaints. At rest, the ventilation per square meter of body surface area was 5.7 L. (normal 5.0 L.). The walking ventilation per square meter was 19 L. (normal 11 L). As would be expected in a patient with a normal metabolic rate and an abnormally high ventilation, the ventilatory equivalent was unusually high (3.4 as compared to a normal of 2.6), a characteristic of so-called "inefficient" respiration. Low blood carbon dioxide tensions and contents (Table II) indicated that this hyperventilation was not restricted to unperfused tissue. In the absence of cardiac disease, hypercapnea, or hypoxia, the cause of the hyperpnea and sensation of breathlessness remained obscure.

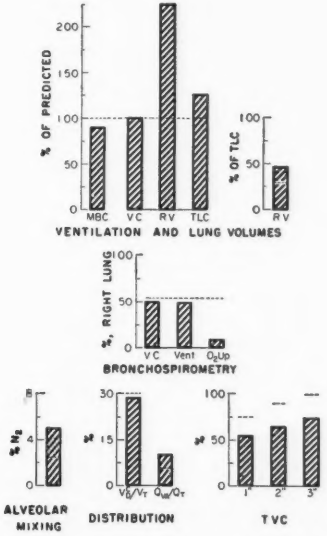


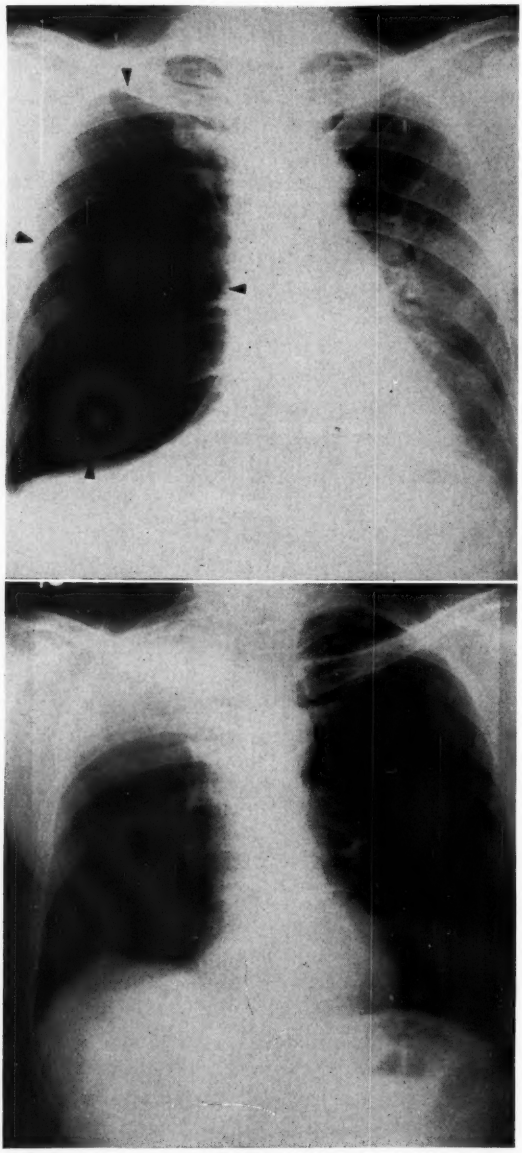
Fig. 3C.—Preoperative function data of Patient 3. The residual volume is high; mixing of respiratory gases within the lung is poor; the dead space and venous admixture ratios are both elevated; and the timed vital capacity is slowed. The contribution of the right lung to oxygen uptake is extremely low.

Summary.—Bilateral studies revealed a high residual volume, a slowed timed vital capacity, and poor intrapulmonary mixing of gases. There was minimal interference with ventilation on the side of the cyst but a pronounced limitation of oxygen uptake. Together with elevated dead space and venous admixture ratios, these abnormalities indicated interference with the function of the ipsilateral parenchyma. Hyperpnea at rest and exercise and the consequently low carbon dioxide tensions and contents in arterial blood remained unexplained.

PATIENT NUMBER FOUR

Clinical Summary.—This 49-year-old white male postal clerk was admitted for progressive episodic dyspnea, palpitations, and right chest pain of three years' duration. These symptoms, occurring only on exertion, were increasing

A.



B.

Fig. 4.—*A*, Chest roentgenogram. Note the increased radiolucency of the entire right hemithorax.

B, Chest roentgenogram five months following excision of right upper lobe cyst and construction of pleural tent.

in frequency from once a week originally to once a day on admission. He had had a chronic cough of 20 years' duration, productive currently of 50 c.c. of white sputum per day.

Physical examination revealed diminished respiratory excursion, increased resonance, and decreased breath sounds throughout the right chest. In the left lung there was prolongation of expiration with expiratory wheezes. There was no clubbing, cyanosis, or edema of the extremities.

X-ray of the chest showed almost complete loss of the usual right lung markings, these being replaced centrally by dense fibrotic-like strands (Fig. 4*A*). The left lung showed localized increased radiolucency in the apical area. The mediastinum shifted to the affected side on inspiration and to the opposite side on expiration. Pulmonary function studies were obtained (Fig. 4*C*).

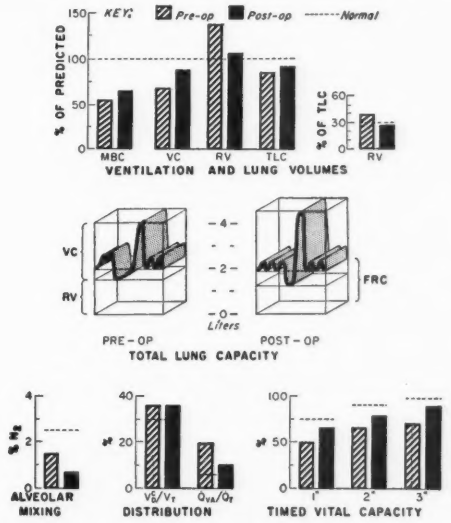


Fig. 4*C*.—Pre- and postoperative function data of Patient 4. Preoperatively there were abnormalities of ventilation, lung volumes, and ventilation-perfusion relationships. Severe obstruction was indicated by the low maximum breathing capacity, the slope of the expiratory tracing, and the slowed timed vital capacity. The normal mixing index suggested poor communication. Most abnormalities were diminished by operation.

On April 28, 1955, a right thoracotomy revealed a cyst originating from the upper lobe and completely collapsing the middle and lower lobes. The cyst could be inflated but would deflate only with extreme difficulty. Since there were also numerous bullae of the apical and posterior segments, the cyst and the right upper lobe were resected. Inasmuch as the remaining pulmonary parenchyma on expansion only partially filled the pleural cavity, the hemithorax was tailored, as described in Case No. 3, with a pleural tent (Fig. 4*B*).

The postoperative course was uncomplicated. Function studies were repeated ten weeks following resection (Fig. 4*C*).

Physiologic Studies.—This patient's large cyst was associated with abnormalities of lung volume, ventilation, and distribution (Fig. 4*C*). The vital capacity was less than 70 per cent of the predicted value. Although bronchospirometry was not performed, inspection, auscultation, and fluoroscopy showed that the contribution of the right lung to respiration was grossly reduced. The physical signs and the normal index of intrapulmonary mixing indicated that the cyst communicated poorly, if at all. That proportion of the intrapleural volume occupied by the cyst could therefore not be measured, for the Darling technique is based on collecting gas (N_2) from air-containing space. Despite the presence of this large space-filling structure, the residual volume of the lungs was moderately elevated, indicating that the patient was unable to reduce the measurable volume of air in parenchyma to a normal minimum by expiring forcefully. Severe obstruction to air flow contributed to this inability. This was indicated by the progressively diminishing slope of the expiratory tracing (inscribed in the volumetric schema in Fig. 4*C*) and by the figures for the timed vital capacity. Failure of the mid-position to be promptly restored following an expiratory effort, shown in Fig. 4*C*, is characteristic of obstructive breathing. In keeping with these findings, the maximum breathing capacity was low.

Ventilation at rest was moderately increased to 5.5 L. per square meter of body surface area (normal 5 L.)—and was high in relation to oxygen uptake, the ventilatory equivalent being 3.2 (the normal range 2.2 to 2.6). In contrast to the previous patient, however, hyperventilation had not resulted in abnormally low arterial carbon dioxide tensions and contents (Table II), indicating that *alveolar* ventilation was proportional to carbon dioxide production.

Both dead space and venous admixture ratios were high, indicating an abnormal relationship between the distribution of gas and blood within the lungs. Since, as concluded from physical signs and mixing index, the cyst remained virtually unventilated, these distribution defects could be ascribed not to the cyst itself but either to the effect of the cyst on ipsilateral parenchyma or to abnormalities of the contralateral lung. Following resection, the arterial saturation at rest rose to normal values and the venous admixture component was restored nearly to normal. Coupled with the improved spirogram and timed vital capacity, these postoperative values suggested that the major portion of the preoperative abnormalities could be attributed to the effect of the cyst on adjacent parenchyma rather than to contralateral pulmonary pathology.

It should be observed, however, that the dead space ratio was unaltered by operation and that some abnormality of arterial blood oxygenation remained; the venous admixture ratio was moderately elevated and the saturation at exercise was abnormally low.

In addition to the favorable effect on oxygenation of arterial blood and on resistance to gas flow during expiration, excision of the cyst was followed by an increase in vital capacity (both inspiratory capacity and expiratory reserve) and total lung capacity and by a fall in the residual volume. Whereas the ratio of the residual volume to the total lung capacity had been abnormally

high preoperatively, it fell to within normal limits postoperatively. The construction of a pleural tent contributed to the fall in residual volume and limited the restoration of the total lung capacity.

The remaining abnormality in maximum breathing capacity, and indeed in the other aspects of function already noted, may be ascribed in part, at least, to the brevity of the patient's postoperative convalescence.

Summary.—This patient, with a large unilateral air cyst, demonstrated severe abnormalities of ventilation, lung volumes, venous admixture, and physiologic dead space. Intrapulmonary mixing was normal. Together with the physical signs, the data were interpreted to indicate very poor communication of the cyst and gross interference with the function of ipsilateral lung. Following excision of the cyst the patient demonstrated more nearly normal lung volumes, reduced resistance to air flow within the airways, and improved oxygenation of arterial blood. The residual abnormalities in lung volumes, ventilation, and distribution were ascribed to incomplete recovery of function in lung which had re-expanded following a protracted period of compression.

PATIENT NUMBER FIVE

Clinical Summary.—This 43-year-old white male writer first entered the hospital on May 20, 1954, with symptoms of one and one-half years' duration of slight to moderate dyspnea on exertion. There had been no orthopnea, cough, or hemoptysis. Pre-employment roentgenograms in January and March of this year had revealed the presence of bilateral pulmonary cysts.

The chest was symmetrical with equal expansion. There were hyperresonance and absent breath sounds in the left infraclavicular space. The extremities exhibited no clubbing or cyanosis.

X-rays of the chest showed two large areas of increased radiolucency involving the left upper lobe and a considerable portion of the right upper lobe. Bronchography revealed marked compression and displacement downward of the left upper lobe bronchi and crowding of the right upper lobe bronchi. Tomography (Fig. 5*A*) demonstrated a large cyst virtually replacing the left upper lobe and multiple cysts of the right upper lobe. Pulmonary function studies were performed (Fig. 5*C*).

On July 14, 1954, left thoracotomy was performed. There was a cyst, 14 cm. in diameter, occupying the apical-posterior segment of the left upper lobe together with three adjacent cysts each approximately 5 cm. in diameter. Incision of the large cyst demonstrated patent connecting bronchi. The cysts were removed by a wedge technique. A pleural tent was created to tailor the remaining pleural space to the volume of the remaining lung parenchyma.

On return to the hospital in November of 1954, the patient had noticed subjective improvement in dyspnea and increased ability to do moderately strenuous work. On Nov. 10, 1954, a right thoracotomy revealed many large, thin-walled multilocular cysts of the apical and posterior segments of the right upper lobe. These were readily filled by positive pressure but deflated extremely slowly when suction was applied to the endotracheal tube. The remainder of the upper lobe contained fibrotic tissue and numerous small cysts.

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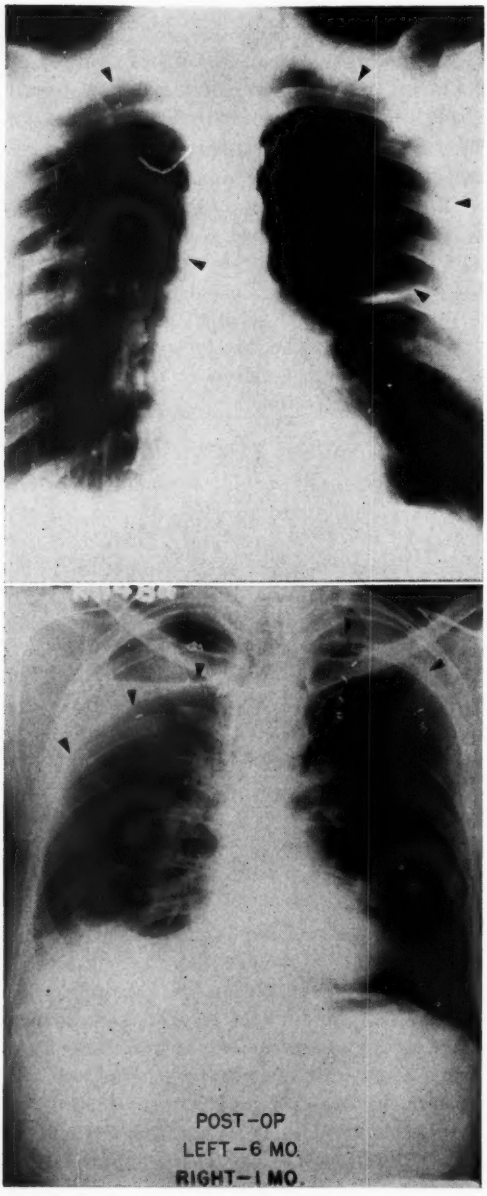
A.



B.

Fig. 5.—*A*, Preoperative tomogram showing bilateral apical radiolucent areas. *B*, Chest roentgenogram following completion of staged resection of bilateral lung cysts. Arrows indicate pleural tents.

A right upper lobectomy was accomplished and a pleural tent constructed (Fig. 5*B*). Lung function studies were reported before and after the second operation (Fig. 5*C*).

Physiologic Studies.—The preoperative values for this patient with extensive bilateral cystic disease were remarkably good. The maximum breathing capacity, vital capacity, total lung capacity, and mixing index were normal or nearly so. The timed vital capacity, however, was definitely slowed, and the residual volume was elevated. There were, therefore, increased resistance to air flow on expiration and inability to reduce the volume of the lungs to a normal minimum by forceful expiration.

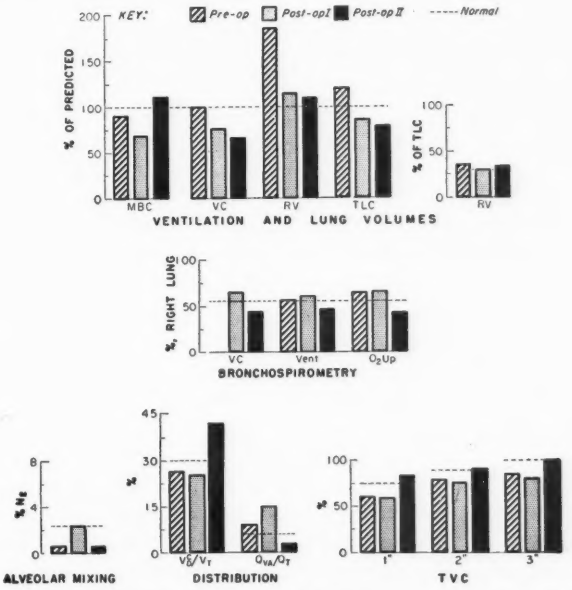


Fig. 5*C*.—Pre- and postoperative function data of Patient 5. In spite of bilateral cystic disease, tests of preoperative function did not disclose striking abnormalities. See text for discussion.

The fact that the index of intrapulmonary mixing was normal indicated that the cysts either did not communicate at all or communicated so completely as to be cleared of nitrogen during the period of oxygen breathing. In the latter instance one would expect the physiologic dead space to be abnormally high. The normal figure for this measurement suggested extremely poor communication. Slowing of the timed vital capacity, therefore, could probably not be ascribed to evacuation of large cystic areas through attenuated orifices. This impression was confirmed at fluoroscopy by the finding that the dimensions of the cysts appeared to remain constant during deep breathing. The slowed timed vital capacity could then be attributed either to obstructive parenchymal disease exclusive of the cysts or, as was more likely in view of the good

maximum breathing capacity, to a regional obstructive effect of the cysts on adjacent tissue. The improvement in maximum breathing capacity which followed excision of the cysts supported the latter explanation.

This patient, as well as the first 2, demonstrated that a poor timed vital capacity is compatible with a good maximum breathing capacity. By performing the latter test with an elevated position of the chest, some patients with obstructive pathology may ventilate well using the portion of their respiratory cycle characterized by the least obstruction.

In addition to improving ventilation (maximum breathing capacity), removal of the cysts produced changes in the lung volumes. The interpretation of these was colored by the space-filling procedures (pleural tents) concomitantly performed. The fall in vital capacity and total lung capacity could be attributed either to thoracotomy or to restriction of the endothoracic space. The striking fall in residual volume was probably a result of the latter, for similar changes do not usually follow uncomplicated bilateral resections.[18]

The results of bronchospirometry before and after the first operation were unusual in that the contribution of the left lung to ventilation and oxygen uptake was not adversely affected by ipsilateral pulmonary resection. This indicated that the tissue excised was relatively functionless and that the operation interfered minimally with the performance of remaining tissue. The second operation, however, reduced the contribution of the right lung to abnormally low levels. Probably, therefore, functioning tissue was excised together with the cyst. The operative note suggested that such tissue had been removed with the cyst.

Between the first and second operations, the index of alveolar mixing more than doubled its preoperative value in spite of the fact that a decrease might have been expected by virtue of the considerable fall in functional residual capacity which followed the first operation. Increased communication of the remaining cysts on the right side was a possible explanation for this change. An x-ray report dated one week following the second study described "less radiolucency at the right apex." This finding, together with reversion of the mixing index to preoperative levels after removal of the right upper lobe, suggested that communication had improved and that poor mixing in the cystic areas had indeed accounted for the high alveolar index.

The variations in distribution ratios are difficult to interpret. There was an increase in venous admixture following the first operation and, after the second operation, a pronounced rise in the ratio of the dead space to the tidal volume. The former indicated that after the first operation a larger proportion of the cardiac output was delivered to alveoli which were poorly ventilated relative to their perfusion. The dead space ratio is sometimes elevated out of proportion to an elevation in venous admixture in patients with emphysema.[19] A similar effect is produced when the Pa_{CO_2} is overestimated due to error in its measurement. This determination was carried out in quadruplicate with good checks. In the absence of an analytical error, the reason for the unusual postoperative pattern of distribution in this patient remained unexplained.

Finally, it should be observed that the improvement in timed vital capacity (Fig. 5*C*) reflected not an increase in the volume of air expelled in 1, 2, or 3 seconds but the considerable decrease in the vital capacity. Indeed, less air was moved postoperatively in each of the 3 time intervals than had been expelled preoperatively.

Summary.—This patient with bilateral cystic disease, in spite of respiratory symptoms, had a good maximum breathing capacity, nearly normal lung volumes, and minimal abnormalities in ventilation-perfusion relationships. The timed vital capacity was definitely slowed, however, and the mixing index was minimally elevated. Although it had been predicted preoperatively that the cysts on neither side communicated well, inspection of the pathologic specimens demonstrated anatomically patent communications on the left. Bilateral resections with construction of pleural tents were followed by an improved maximum breathing capacity, better intrapulmonary mixing, a fall in the major volumetric compartments, and relief of subjective symptoms.

PATIENT NUMBER SIX

Clinical Summary.—This 31-year-old Negro man first noted the onset of pain in the right upper chest and progressive exertional dyspnea in March of 1953. Past history and systemic inquiry were noncontributory except for an episode of spontaneous pneumothorax of the left lung in 1951.

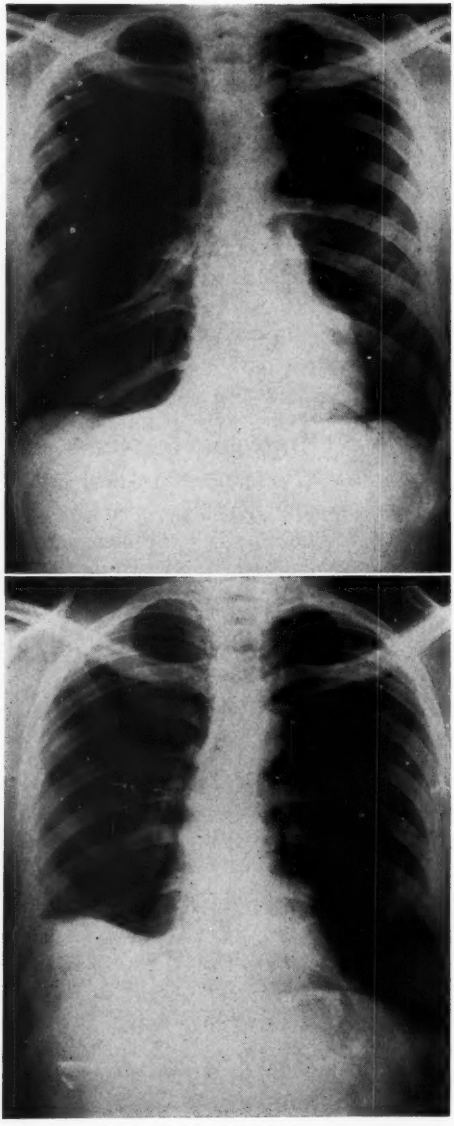
Physical examination disclosed diminished expansion of the chest. Tactile fremitus, vocal fremitus, and breath sounds were absent from the right upper chest both anteriorly and posteriorly. There were râles at the right base, posteriorly. Roentgenographic examination of the chest revealed a large air-containing cyst in the right lung (Fig. 6*A*). Pulmonary function studies were obtained (Fig. 6*C*).

At thoracotomy, on Aug. 4, 1953, the pleural space was found to be completely obliterated by adhesions. It was impossible to collapse the lung because of the presence of innumerable large cysts in which the air was trapped. The cysts, varying from the size of a "football" to that of a "match head," were almost all located in the right upper lobe. They were removed by wedge resection.

Postoperative chest roentgenograms (Fig. 6*B*) revealed one large and several smaller cysts in the left lung, these having become apparent following the contralateral surgery. Further pulmonary function studies were obtained (Fig. 6*D*).

On Sept. 24, 1953, a left thoracotomy disclosed a large thin-walled, air-containing cyst which immediately ballooned out through the incision. This cyst, measuring 12 by 8 cm., was attached to the anterolateral edge of the lingula. There were also three "lemon-sized" cysts arising from the midanterior portion of the left upper lobe and multiple smaller cysts and emphysematous blebs scattered throughout the remaining parenchyma. The left lower lobe was grossly normal except for the presence of small emphysematous blebs. The

A.



B.

Fig. 6.—*A*, Chest roentgenogram. Note large radiolucent area occupying the upper half of the right hemithorax.

B, Chest roentgenogram. Right lung cyst has been excised. Note the appearance of the radiolucent area in the left hemithorax.

larger cysts were removed by wedge resection with the pleura being approximated over the exposed lung tissue. Large bronchi were encountered in the resection of the cysts.

The postoperative course was uneventful. Following convalescence after the second thoracotomy, the patient was capable of moderate exertion without feeling short of breath.

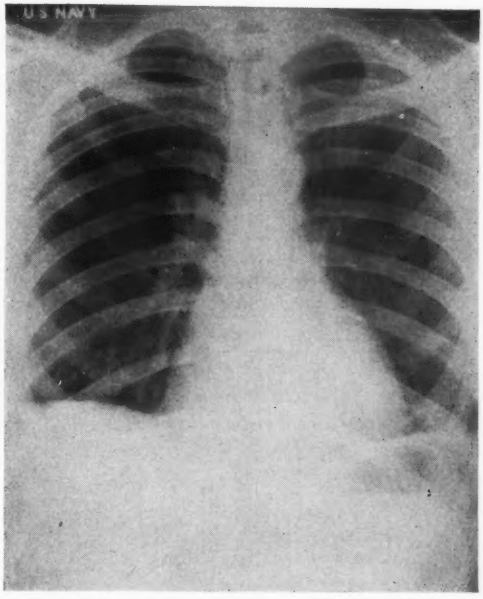


Fig. 6*C*.—Chest roentgenogram. Appearance of chest following bilateral excision of lung cysts.

Physiologic Studies.—In contrast to the previous patient with bilateral cystic disease, the present one demonstrated a number of obvious respiratory abnormalities. The maximum breathing capacity, vital capacity, and total lung capacity were reduced. The contribution of the right lung to function was abnormally low (less than 35 per cent of total). The mixing index was moderately elevated. The venous admixture was extremely high and the maximum diffusing capacity was very low.

Postoperatively, the values for all tests were more nearly normal. Ventilation, lung volumes, intrapulmonary mixing, arterial blood gas contents, and dimensions of the alveolar-capillary bed (maximum diffusing capacity) were all favorably affected. Therefore, a major portion of the preoperative respiratory pathology could be ascribed to the effects of the cysts rather than to other parenchymal disease. Preoperatively most of the right lung was compressed into the right lower chest (''vanishing lung syndrome'') and could

not normally circulate either air or blood. Ventilation and mixing were therefore poor and the measurable lung volumes were small. Perfusion remained more nearly normal than ventilation with the result that an unusually large proportion of the blood flowing through the lungs was poorly oxygenated.

Saturation of peripheral arterial blood with oxygen was therefore low (92 per cent at rest, 88 per cent during steady-state treadmill exercise), and the venous admixture ratio was unusually high (24 per cent). Carbon dioxide content (46.92 vol. per cent) and tension (35 mm. Hg), however, were low in contrast to what one might expect in a mixture containing 24 parts of mixed venous blood and 76 parts of well-arterialized blood. The explanation for this

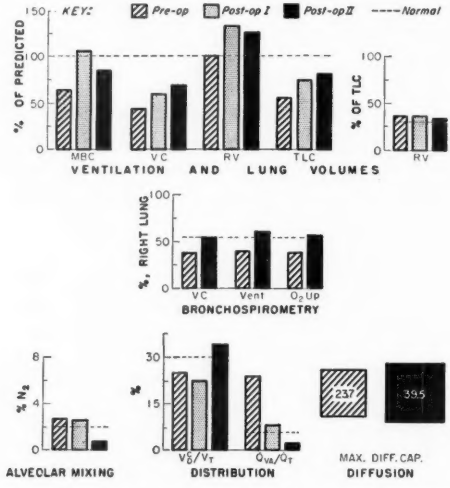


Fig. 6*D*.—Pre- and postoperative function data of Patient 6. Preoperatively there were severe abnormalities of ventilation, lung volumes, relative performance of the two lungs, ventilation-perfusion relationships, and the maximum diffusing capacity. With the exception of the physiologic dead space, all aspects of function were favorably affected by operation.

apparent physiologic discrepancy can be visualized by reference to the differences in the dissociation curves for carbon dioxide and oxygen. These curves show that although it is not possible to augment the arterial oxygen content by regional hyperventilation (flat part of O_2 dissociation curve where increases in P_{O_2} result in only small changes in O_2 content), lowering alveolar P_{CO_2} by this mechanism will cause a loss of CO_2 from the blood. Regional hyperventilation, although ineffective in compensating for poor oxygenation due to localized hypoventilation, is more nearly effective in maintaining normal blood levels of carbon dioxide.

Saturation of peripheral arterial blood is maintained in part by constriction of pulmonary vessels in response to hypoxia.[20] It is evident that, in this patient, this mechanism for shunting blood away from the hypoventilated areas was incompletely effective.

The low diffusing capacity together with the postoperative rise in this measurement suggested that a number of alveolar-capillary units were ineffectual as a result of the cysts' pressures. It should be noted that even postoperatively the value for this test was less than normal. This could be attributed to excision of functioning alveoli contiguous to the cysts, to incomplete postoperative recovery of function, and to the presence of additional small blebs representing destruction of alveoli. The latter were described in the operative note.

Most of the functional improvement was produced by the first operation and may be accounted for by re-expansion of compressed lung. The residual volume was increased because the contents of the entire right hemithorax now contributed to the functional residual capacity; preoperatively, a large proportion of the intrapleural volume had been filled by the noncommunicating air-filled cysts. The maximum diffusing capacities after the first and second operations were nearly identical, indicating that the tissue excised from the left lung at the second operation included a minimum number of functioning alveoli. As was true of the diffusing capacity, persistence of low values for tests of ventilation and lung volumes reflected in part the effect of the short convalescence. Finally, the poor communication suggested preoperatively by the mixing indices was confirmed at thoracotomy.

Summary.—This patient with bilateral air cysts and severe respiratory abnormalities improved strikingly after excision of the cysts permitted re-expansion of compressed lung. The improvement was measured in terms of ventilation, lung volumes, intrapulmonary mixing, ventilation-perfusion relationships, and the total maximal area of the effective alveolar-capillary bed. The preoperative prediction that the cysts on both sides communicated poorly was borne out at thoracotomy. The respiratory deficits remaining postoperatively were attributed to both the brevity of the patient's convalescence and the remaining pulmonary pathology.

DISCUSSION

The six studies of pulmonary cystic disease included in this report were selected (1) to serve as interesting exercises in the interpretation of pulmonary function tests, (2) to demonstrate the variability in the physiologic deficit associated with cystic disease of the lung, and (3) to document the beneficial effects of excisional therapy.

The first objective was approached by illustrating and discussing the patients' performance of certain pulmonary function tests.

With reference to the second and third objectives, these studies show that no single pattern of respiratory abnormality is characteristic of pulmonary cystic disease. Large cysts may be associated with a minimal, moderate, or extreme physiologic deficit incorporating not only abnormalities of ventilation and lung volume but of gas exchange as well.

In the absence of generalized pulmonary disease, the degree of the physiologic abnormality produced by a cyst is largely a function of the extent to which the cyst compresses the surrounding lung. This compression in turn is

greater as the pressure difference between the inside of the cyst and the adjacent tissue increases. When a cyst communicates poorly or intermittently (Patients Nos. 4 and 6), this pressure difference remains high. Particularly on forced expiration, the cyst remains inflated at a high intracystic pressure at a time when the adjacent parenchyma contains its residual volume at oral or atmospheric pressure. The patency of communication, therefore, is a critical factor in the production of parenchymal compression. Accordingly, the index of alveolar mixing, an approximate measure of the degree of communication, is of particular significance.

As would be expected from the foregoing, those patients with the most severe physiologic deficits had, as judged from normal or minimally elevated alveolar indexes, poor or intermittent communication. In these, the effect of the cyst's pressure was not only to obstruct the flow of air to and from adjacent tissue but, in addition, to disrupt the normal relationship between ventilation and perfusion of this tissue. In Patient No. 6, for example, pre- and postoperative measurements of the maximum diffusing capacity showed that the number of alveoli available for the diffusion of oxygen into the blood stream was in effect diminished. These derangements together with abnormal ventilation-perfusion relationships and an attenuated diffusing surface are those one would expect in a lung in which partial and complete atelectasis were mixed. They fit the interpretations of roentgenograms and the descriptions of the lung at thoracotomy.

None of the patients had physiologically compromising generalized pulmonary emphysema. Two (Nos. 4 and 6), however, demonstrated hypoxia (excessively high venous admixture ratios) both at rest and exercise. In both instances, the saturation of arterial blood at rest returned to normal postoperatively and, in one instance (No. 6), to normal levels even on severe treadmill exercise. Poor saturation of arterial blood per se, therefore, was not an absolute contraindication to surgery. This point is stressed because of the emphasis it is given by Baldwin and her colleagues.[1] Among the 16 patients reported by these authors, hypoxia was found only in patients in whom cystic disease was superimposed on advanced pulmonary emphysema. Hypoxia under this circumstance is undoubtedly an adverse prognostic index. It is evident from the present patients that hypoxia may appear independently of emphysema. One would have excluded from surgery those patients who were to gain the most from it, had poor saturation of arterial blood in itself been interpreted to contraindicate resection.

The patient with far-advanced emphysema is, of course, a poor surgical risk and should be distinguished from one whose respiratory deficits can be ascribed primarily to cysts and their effects on relatively normal adjacent parenchyma. This distinction may be difficult, for the physiologic characteristics of each disease have much in common. However, in the 2 patients (Nos. 4 and 6) whose poor saturation of arterial blood might have led one to suspect advanced emphysema, other findings did not confirm this impression. The alveolar index was not high; the ratio of the residual volume to the total lung

capacity was not unusually elevated; and there was no carbon dioxide retention. Physical findings and roentgenography, of course, are also of additional help in establishing the presence of generalized emphysema.

The correspondence between preoperative physiologic evidence of communication and the ease with which the cyst could be deflated at operation was good. The difference between physiologic and anatomic communication was demonstrated by Patient No. 3 whose specimen showed a number of patent airways despite evidence of poor functional communication. A valve mechanism at the orifices within the cyst is a possible explanation for this apparent inconsistency.

It is our opinion that the surgical treatment of few pulmonary lesions offers a more promising functional result than that demonstrated by these patients. As with a constricting pleural peel, the pulmonary cyst is largely functionless and the compressed adjacent tissue may be relatively normal. Optimal results may be expected when treatment is instituted early, for it is reasonable to assume that recovery of parenchymal function is adversely affected by duration and extent of compression.

SUMMARY

The physiologic data of 6 patients with cystic disease of the lung were selected for presentation. The effects of surgical management were studied in 3 of these patients, 2 of whom had bilateral resections. Measurements of ventilation-perfusion relationships, of the maximum diffusing capacity, and of the total capacity of each lung individually were used to supplement the customary bilateral and bronchospirometric determinations of ventilation, lung volume, or oxygen uptake.

Four of the patients fell into recognized functional types: minimal or moderate abnormalities of ventilation and lung volumes with or without evidence of communication between the cyst and airways. Two patients presented patterns of physiologic abnormalities not previously described: severe abnormalities of ventilation, lung volumes, and arterial blood gas contents unassociated with generalized pulmonary emphysema.

In the absence of generalized emphysema, the patency of communication and the degree of parenchymal compression produced by the cysts appeared to be the most likely factors accounting for variation in the physiologic deficit. The preoperative impression of the extent of communication and compression correlated well with the anatomic findings.

Resection of the cysts produced beneficial symptomatic and physiologic effects. In the most severely ill patients, dyspnea was relieved, ventilation improved, lung volumes were restored toward normal, hypoxia was eliminated, and the maximal dimensions of the effective alveolar-capillary bed were augmented.

Patient No. 6 was operated upon by Dr. Melvin Newman whose cooperation in referring the patient for study is gratefully acknowledged.

The clinical analyses, lung volumes, and tests of ventilation were performed by hospital corpsmen of the United States Navy trained in the Cardiopulmonary Laboratory of the United States Naval Hospital, St. Albans, New York. The authors are particularly indebted to the following for their skill and interest: Jerry Borrelli, Henry Haddad, Joseph Malin, John O'Brien, Robert Obser, Ernest Picknally, and Robert Rauf.

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CHRONIC (HEALED) DISSECTING ANEURYSMS

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DISSECTION of the aorta has come to be characteristically associated with the sudden onset of tearing pain, frequently radiating, followed by loss of consciousness, prostration, shock, coma, and death. This dramatic clinical concept of dissecting aneurysms, referring as it does to the acute variety, only tends toward obscuring the fact that a small proportion of this type of aneurysm attempts a healing response to this poorly understood type of mural arterial alteration.

A review of a large number of cases of dissecting aneurysm which have come to autopsy at this Center disclosed five examples of the so-called "healed" variety. It is the purpose of this report to present the clinical and pathologic manifestations of these cases in detail. We feel that the pathologic changes within the aorta, of this series, exhibit the wide range of reparative phenomena that is possible, extending from imperfectly organized intramural hematomata to long-standing secondary endothelial-lined channels with mural elastification and intimal hyperplastic changes. Additional interest obtains in cases of this type by reason of the great advances in the field of cardiovascular surgery, several reports of surgical repair of dissecting aneurysm being found in the recent literature.[1-4]

Some of the data relevant to these cases are outlined in Table I.

TABLE I. SUMMARY OF CASES

CASE NUMBER	AGE	SEX	DURATION LIFE	HEART WEIGHT	TERMINAL BLOOD PRESSURE	CAUSE OF DEATH
1.—R. L. (A55-20)	87	M	>6 mo.	780 Gm.	118/88	Acute dissection of aorta into pericardial space
2.—A. M. (UA40-24)	38	F	1 year	600 Gm.	LA—260/150 RA—200/146	Chronic rheumatic heart disease with failure
3.—A. P. (A55-29)	72	M	7½ mo.	515 Gm.	180/130	Congestive heart failure
4.—L. L. (A48-199)	43	M	63 days	LV—20 mm. RV— 6 mm.	180/110	Aortic rupture into left pleural space
5.—V. E. (A53-229)	86	F	Years	345 Gm.	220/110	Carcinoma of the stomach with metastases

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CASE REPORTS

CASE 1.—R. L. (A55-20), an 87-year-old white man, was apparently well until approximately Jan. 23, 1955, when a diagnosis of coronary artery occlusion was made. He was not hospitalized and it is not known whether an electrocardiogram was obtained.

Two weeks later he was admitted to Syracuse Memorial Hospital complaining of substernal pain, weakness, and a cold-sweating feeling. An accurate past history could not be obtained. Physical examination disclosed an elderly man who was extremely pale, clammy, and in acute distress. Respiratory distress was present. The temperature was 97° F., pulse 126 per minute, and the respirations were 30 to 32 per minute. An 8 by 10 cm. soft, mobile mass was noted in the left neck which pushed the trachea to the right of the midline but did not pulsate. Dullness to percussion was described in the left axilla and base of the left chest and râles were heard at both lung bases. The left border of cardiac dullness was found to be in the left midaxillary line. The heart sounds were of poor quality and a tic-toc rhythm, with some irregularities, was noted. A Grade II

Fig. 1.—Case 1. Aortic intimal surface showing the two clot-filled defects, the larger being more proximal. The central intimal zone to the right of the distal defect is free of atherosclerosis.

precordial systolic murmur and a questionable diastolic murmur were heard in the left axilla. The abdomen was soft and the liver edge could be outlined 1 to 2 fingerbreadths below the right costal margin. The lower extremities were not remarkable. Laboratory data revealed a hemoglobin of 12.5 Gm. per cent; hematocrit, 36 per cent; and a total white blood cell count of 25,000 per c.mm., wth 38 per cent polymorphonuclear leukocytes and 21 per cent lymphocytes. Electrocardiographic changes were interpreted as acute ischemia and injury to the anterolateral septal area with subendocardial ischemia. The patient died on the day of admission.

At autopsy the principal findings were confined to the heart and the aorta. The heart weighed 780 Gm. due to a left ventricular thickness which was twice normal. The valves were not unusual but there was a fibrotic area in the posterior left ventricle consistent with an old myocardial infarction. The aorta was the site of a recent and an old dissection. The old dissection was located in the thoracic aorta while the recent one was

in the ascending portion of the arch with rupture into the pericardium and death was due to cardiac tamponade. This recent dissection was not contiguous with the older process and there was no evidence of an intimal tear. The recent dissection involved the innominate artery but the left common carotid and left subclavian arteries were spared. The healed aneurysm was located in the proximal descending aorta and presented an hourglass-shaped defect which began just below the origin of left subclavian artery. This deformity was oriented in the longitudinal plane of the aorta, measured 15 by 4.5 cm., and appeared to involve 180 degrees of the posterolateral aortic circumference. Viewed from its intimal surface, there were two large defects present (Fig. 1). The more cephalad defect was a shell-shaped 7 by 4 cm. depression filled with impacted blood clot. The second defect was oval in shape, measured 3.5 by 2 cm., and was located 5.5 cm. distal to the lower border of the proximal rent. A sagittal section of this entire area disclosed that although there had once been continuity of intramural hematoma between these tears, it was now nearly obliterated by dense fibrotic tissue which produced the constriction in the hourglass deformity (Fig. 2). The clot within the more caudad depression was easily removed and there appeared to be a nearly complete endothelial lining about this clot. Examination of Fig. 1 gives the impression that the new endothelium was continuous with a pearly-white longitudinal zone that extended distally for a distance of 12 cm.

Fig. 2.—Case 1. Sagittal section illustrating the central organization producing the "hourglass" deformity.

Microscopic examination of the area of recent dissection showed very slight evidence of Erdheim's cystic medionecrosis. Minimal atherosclerosis was present. Study of the old dissection disclosed fibrosis of the entire thickness of the aortic wall in the vicinity of the proximal tear. The intramural hematoma was composed of amorphous eosin-staining material without evidence of significant organization or cellular debris. The vasa vasorum were thickened and there was a prominent lymphoid infiltrate present. The most narrowed point shown in Fig. 2 was composed of dense connective tissue with many prominent large vessels and the overlying intima at this point was the site of marked atherosclerosis. The aortic wall below the distal defect showed mural fibrosis in its outer third only. Of considerable interest was the fact that the most severe cystic medionecrosis was located beneath the intima described previously as a pearly-white longitudinal 12 cm. zone distal

to the more caudad intimal tear (Fig. 3). This area was unusually striking in the gross examination since it was virtually free from atherosclerosis although this process was quite severe along its lateral limits. Since this dissection could not be accurately dated, its duration (more than 6 months) was estimated by comparing the microscopic alterations in this case with others in which the original date of dissection was known.

Fig. 3.—Case 1. Severe cystic medionecrosis in the atherosclerotic-free intima shown in Fig. 1. (×100.)

CASE 2.—A. M. (UA40-24), a 38-year-old white woman, entered Syracuse University Hospital of the Good Shepherd April 9, 1940, complaining of weakness, anorexia, nervousness, intermittent precordial pain, a cough of 6 months' duration, and some swelling of the extremities. She was said to have had coronary artery thrombosis one year previously, with an accompanying fall in blood pressure. Since that time she had noticed occasional sharp precordial pain with radiation to the left arm.

Physical examination disclosed a blood pressure in the left arm of 260/150 mm. Hg and 200/146 mm. Hg in the right arm. The patient was dehydrated, cyanotic, and responded very slowly. The pupils reacted porly to both light and accommodation and the left pupil was larger than the right. Venous congestion was apparent. The heart was enlarged both to the right and to the left as determined by percussion. Loud presystolic, systolic, and diastolic murmurs were heard over the mitral area and a systolic murmur was noted over the tricuspid area. The sounds were of poor quality and the rhythm was totally irregular. A few râles were heard at the base of the left lung, and the liver was located 5 fingerbreadths below the right costal margin and was described as tender and pulsating. Deep tendon reflexes were more active on the right.

Laboratory data disclosed the Wassermann reaction to be negative. The hemoglobin was 11 Gm. per cent; red blood cell count 3.8 million per c.mm., white blood cell count was 38,400 per c.mm., with 96 per cent polymorphonuclear leukocytes, 3 per cent lymphocytes, and 1 per cent monocytes. The urine examination disclosed it to be acid, with a specific gravity

of 1.022, a 4 plus albumin and clumps of both red and white blood cells were seen on microscopic examination. The nonprotein nitrogen was 125 mg. per 100 c.c. The electrocardiogram was interpreted as showing left ventricular preponderance, auricular fibrillation, and myocardial damage. Roentgenographic examination of the chest disclosed the greatest diameter of the chest to be 26 cm., the greatest diameter of the heart to be 20 cm., and there was marked widening of the heart shadow due to left ventricular hypertrophy. The left auricular appendage was not prominent. The trachea deviated to the right posterior and there was some fullness of the supracardiac shadow. There was increased density lateral to the aortic shadow and above each root. These areas lateral to the aortic shadow were thought to be due to congestion, inflammation, or possibly tumor. The patient died on the third day after admission.

At autopsy, there was evidence of acute and chronic rheumatic heart disease, mitral stenosis, a mural thrombus in the left auricular appendages, left ventricular hypertrophy (heart weight—600 Gm.), chronic passive congestion of the liver, arteriolar nephrosclerosis, bronchopneumonia, and focal glomerulonephritis. Permission for examination of the brain was not obtained. Examination of the aorta disclosed it to be enormously widened from the distal end of the arch to the iliac bifurcation. Inspection of the aortic interior revealed the presence of two distinct lumens at the distal end of the aortic arch leading into a so-called "double-barrel" aortic structure (Fig. 4). The larger lumen was continuous with an intramural secondary channel which had been produced by a previous aortic dissection. This secondary passage extended down the length of the aorta to terminate in the left iliac artery where it recommunicated with the original vascular system. The lining of this secondary channel was light yellow, somewhat wrinkled, and contained organized intimal thrombi which extended from its origin to a point just below the celiac axis. Moderate atherosclerosis was present within the true lumen.

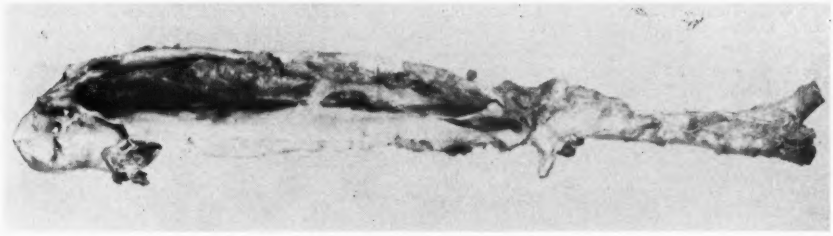

Fig. 4.—Case 2. Double-barrel aorta with both channels only partially opened. The false channel contains organized blood clot.

Microscopic examination of the true aortic wall disclosed a moderate amount of cystic medionecrosis within the ascending aorta and aortic arch while the process was virtually absent within the thoracic and abdominal aorta. Atherosclerosis was diffusely present along the entire length of the true aortic intima. The secondary channel was characterized by a thick wall, a new endothelial lining, and by marked subintimal proliferation. With the use of Verhoeff's elastic stain a large number of new elastic fibers were noted to have developed within the wall of the secondary channel (Fig. 5). The most striking abnormality, however, was the large number of focal, eccentrically located zones of intimal thickening. Although devoid of elastic tissue, they were composed of an embryonic type of loose mesenchymatous tissue very similar to that seen in Wharton's jelly of the umbilical cord (Fig. 6). The fibroblasts within these subintimal thickenings were stellate-shaped and there was a large amount of pale homogeneous intercellular substance which appeared almost fluid in nature. Although several observers have described the presence of arteriosclerosis within the secondary channel,[5-7] we failed to see any similarity between this type of intimal change and any variant of human arteriosclerosis. It did, however, appear to be identical with the changes described by Prior and Jones,[8] who noted

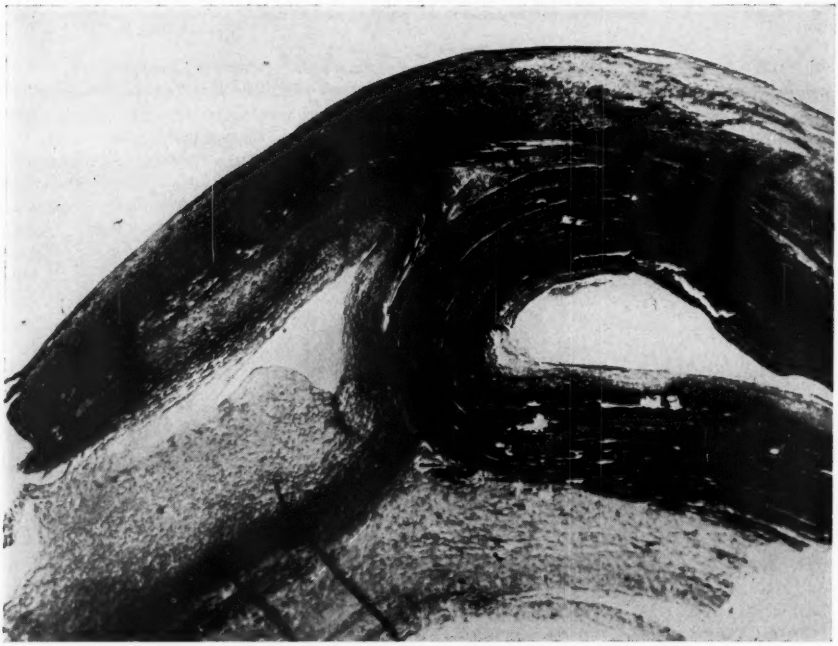

Fig. 5.—Case 2. Verhoeff's elastic tissue stain showing new elastic tissue formation in the secondary lumen toward the left side of the illustration. The new intimal connective tissue in this channel can be seen. (×20.)

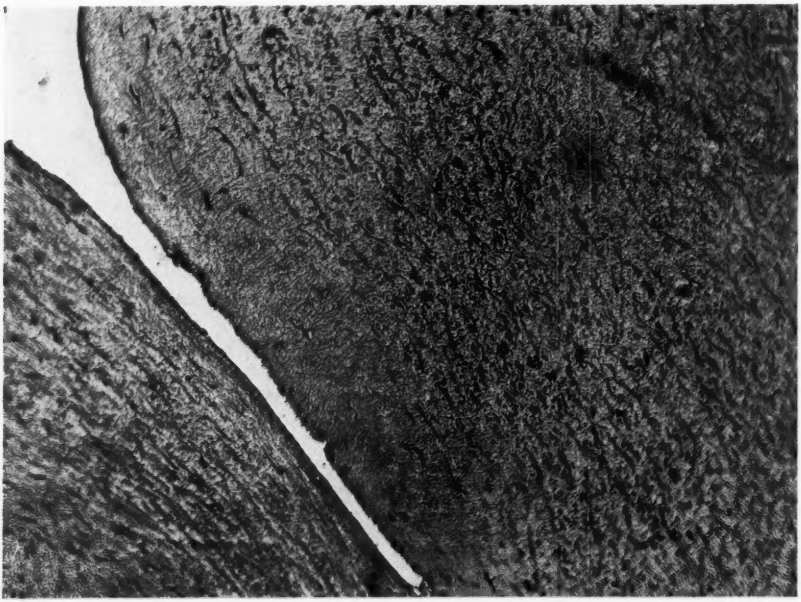

Fig. 6.—Case 2. Higher-power magnification of the newly formed intimal and subintimal connective tissue within the secondary channel. (×65.)

persistence of mesenchyme-like structure within the aortic intima and within the intima and media of the great vessels arising from the arch at birth, and for a considerable length of time thereafter in the newborn infant.

CASE 3.—A. P. (A55-29), a 72-year-old white man, was well until June 19, 1954, when he complained of continuous subxiphoid pain. The first pain appeared suddenly and while he was at rest. Additional complaints of exertional dyspnea, paroxysmal nocturnal dyspnea and two-pillow orthopnea were elicited by the examiner. The pain disappeared on July 12, 1954, and hypertension was first noted one month later. A roentgenogram of the chest taken Jan. 5, 1953, prior to the onset of symptoms, was interpreted as showing slight mediastinal widening. A subsequent roentgenogram taken on Aug. 13, 1954, after the onset of symptoms, showed enlargement of the heart and a dilated tortuous aorta. No pleural fluid was seen but there was some pulmonary vascular congestion indicating heart failure.

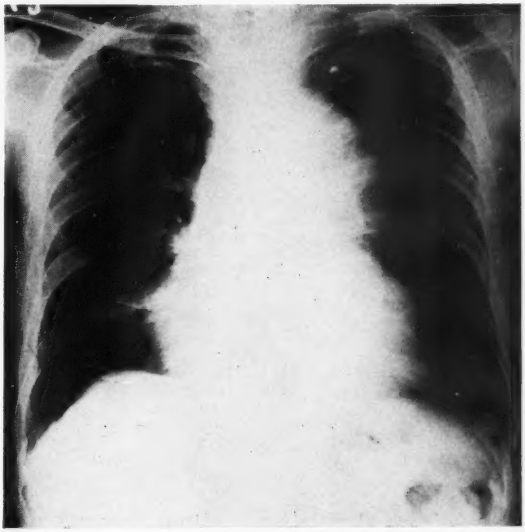

Fig. 7.—Case 3. Chest roentgenogram showing the peculiar segmental flattened appearance of the convex aneurysmal surface.

Six weeks later, on Sept. 27, 1954, this patient was admitted to Syracuse University Hospital of the Good Shepherd complaining of shortness of breath and inability to sleep for the preceding week. The symptoms of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea persisted. He was digitalized at this time and maintained on 0.1 Gm. of digitalis leaf daily. The blood pressure on admission was 200/134 mm. Hg. Diffuse inspiratory coarse râles were heard over both lung bases. The heart was slightly enlarged to percussion and the liver was 2 fingerbreadths below the right costal margin in the midclavicular line. No mention of an absent pulse in any extremity was made. A roentgenogram of the chest and fluoroscopic studies showed a dilated tortuous aorta at this time (Fig. 7). The Wassermann reaction was negative and other laboratory data were noncontributory. An electrocardiographic examination was interpreted as showing left ventricular enlargement. The patient was discharged Oct. 29, 1954, without signs of cardiac failure.

Additional chest roentgenograms were taken in the outpatient department on Dec. 30, 1954, approximately six and one-half months after the onset of symptoms. The heart remained slightly enlarged and the lungs were clear. There had been further

widening and elongation of the aortic shadow. No localized aneurysm was noted. The patient was fluoroscoped also and the final impression was that the aorta was arteriosclerotic, but because of the rapid increase in size, the possibility of dissection was suggested.

On Feb. 1, 1955, approximately seven and one-half months after onset of symptoms, the patient entered Syracuse General Hospital. During the previous month his dyspnea

Fig. 8.—Case 3. Intimal aortic surface showing the two clot-filled intimal defects. The transverse laceration to the right of the distal defect is an artefact.

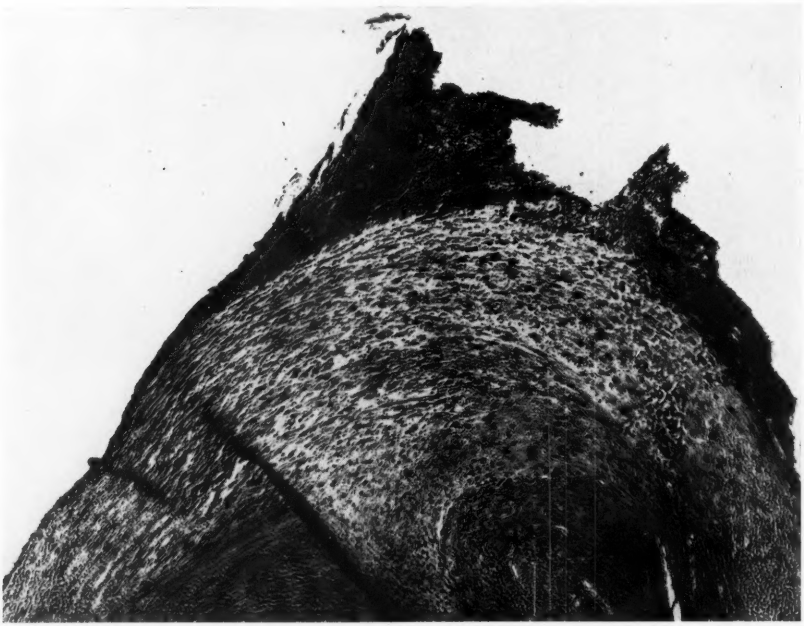

Fig. 9.—Case 3. Active intimal fibroblastic growth occurring about the proximal defect and extending into the blood clot. (×95.)

had become worse but there was no history of recent chest pain. The blood pressure at this time was 180/130 mm. Hg. Inspiratory râles were heard throughout both lungs and the heart sounds were faint. The record states that the patient's heart began to fibrillate, the blood pressure dropped to 80/56 mm. Hg and death occurred on Feb. 3, 1955.

At autopsy the significant findings included pulmonary edema, bilateral hydrothorax, bronchopneumonia, a benign duodenal ulcer with pancreatic penetration, left ventricular hypertrophy (heart weight—515 Gm.), and arteriolar nephrosclerosis. The thoracic aorta was the site of a fusiform dilatation measuring 19 by 5 cm. and encompassing 180 degrees of the posterolateral aortic circumference. This aneurysm began 4.5 cm. distal to the left subclavian artery and terminated 8 cm. above the coeliac axis. Viewed from the intimal surface there was a complete separation of intimal continuity just below the left subclavian artery (Fig. 8). The narrow portion of this intimal tear measured 1 cm. in length, while the widest portion took the form of a transverse oval defect measuring 5 by 2 cm. Both of these defects were filled with clotted blood. The distal intimal tear was circular in shape, had ragged margins, was filled with clotted blood, and measured 3 cm. in diameter. A triangular-shaped pearly-white intimal surface similar to that described in Case 1 extended for a distance of 4 cm. below this distal defect. Atherosclerosis was not present on this intimal surface. A separate intramural hematoma, measuring 1.5 by 2.5 by 2.5 cm., was noted at the level of the coeliac axis. This area showed no evidence of intimal rupture but did encroach upon the coeliac axis, right renal, and superior mesenteric arteries.

Microscopic examination of the aortic arch proximal to the tear revealed a thickened adventitia, intimal atherosclerosis, and no evidence of cystic medionecrosis. Sections taken from the area of the proximal tear showed marked intimal reparative activity (Fig. 9). The fibroblasts were characterized by pyknotic nuclei and showed active invasion of the clot. Verhoeff's elastic tissue stain revealed very scant amounts of elastic tissue within the newly formed, thickened intimal tissue. This intimal proliferation was histologically identical with experimental regeneration of the intima of the rabbit aorta as described by Prior and Hutter,[9] occurring about thirty-five days after intimal injury. The intramural clot was composed of acellular, amorphous, acidophilic debris, and organization of this material was proceeding very slowly from the outer coat of the aorta. The intima about the distal tear showed the same pattern of organization as described above in association with the proximal defect. The pearly-white appearance of the triangular-shaped intimal segment below the distal tear was caused by severe underlying cystic medionecrosis. The distal separate intramural hematoma appeared to be of more recent origin than the larger clot but showed intimal and adventitial connective tissue invasion into the hematoma.

Case 4.—L. L. (A48-199), a 43-year-old white male farmer, was in good health until June 29, 1948, when he suffered the sudden onset of severe substernal pain during effort. He was immediately hospitalized and at that time the blood pressure was recorded as 230/170 mm. Hg in both arms. The temperature, pulse, and respirations were within normal limits. The pain persisted for four days and was characterized by infrascapular radiation. Laboratory data at this time revealed a total white blood cell count of 30,000 per c.mm., with 90 per cent polymorphonuclear leukocytes and 10 per cent lymphocytes. The red cell count was 8 million per cubic millimeter with 19 Gm. of hemoglobin. An electrocardiogram was stated to show left axis deviation. One week after hospitalization the blood pressure in both arms was 270/120 mm. Hg and the level in the legs was slightly lower. On July 8, 1948, eleven days after the acute episode, the blood pressure was not obtainable in the legs and they were cold and mottled blue-red in color. No arterial pulsations were present. A phlebotomy of 500 c.c. was carried out, following which warmth gradually returned to the legs, and the blood pressure was then recorded as 160/140 mm. Hg in both lower extremities.

The patient was transferred to Syracuse University Hospital on July 16, 1948, for further study. The patient was semiconscious and exhibited Cheyne-Stokes respiration. The blood pressure was 235/130 mm. Hg in both legs. Pertinent physical findings at this time

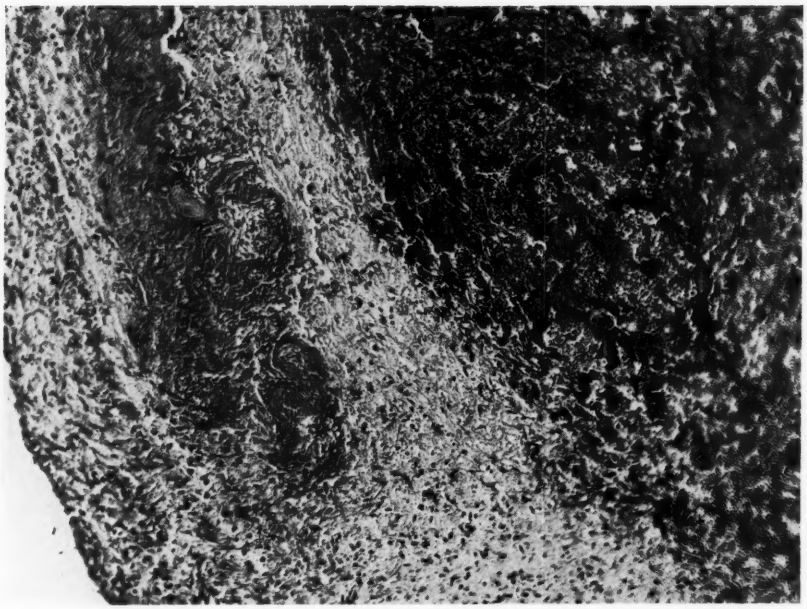

Fig. 10.—Case 4. Intimal and subintimal "granulation" type tissue with abundant new capillaries. The ruptured medial layer is noted in the left portion of the photomicrograph while the blood clot occupies the upper right half of the illustration. (×65.)

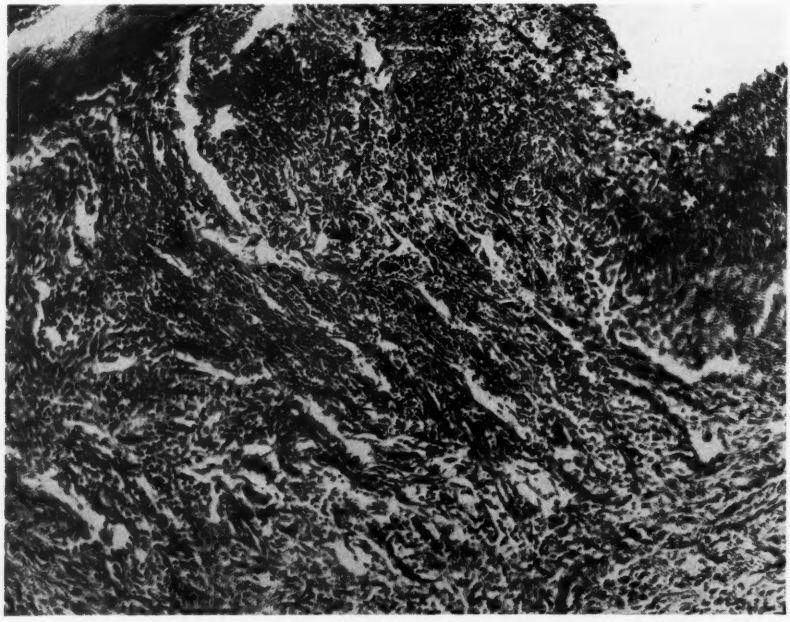

Fig. 11.—Case 4. Active granulation tissue invading the hematoma from the adventitial surface. (×70.)

were minimal arterio-venous nicking, old white exudate in the right fundus, cardiac enlargement, and a systolic murmur along either side of the upper thoracic spine. The red blood and white blood cell counts were unchanged from the previous examination. An electrocardiogram disclosed left axis deviation, horizontal position of the heart, and digitalis effect. Roentgenogram of the chest showed left ventricular enlargement, enlargement of the arch of the aorta with increased tortuosity. The colloidal gold test on the spinal fluid was negative. During his hospital stay the patient received aminophylline, penicillin, paraldehyde, and a low sodium diet. On this regime the blood pressure in the arms dropped to 180/110 mm. Hg while the blood pressure in the legs remained at about 170/130 mm. Hg. The patient was discharged on July 30, 1948, with a tentative diagnosis of malignant hypertension, possible dissecting aortic aneurysm, and possible periarteritis nodosa. The patient died suddenly a few hours following discharge.

At autopsy, the significant findings included a left hemothorax, atelectasis of the left lung, patchy areas of myocardial fibrosis, chronic passive congestion of the liver and spleen, and arteriolar nephrosclerosis. The heart showed left ventricular hypertrophy, the left ventricle measuring 2 cm., and the right measuring 0.6 cm. in thickness. Inspection of the interior of the aorta disclosed an intimal tear located just distal to the origin of the left subclavian artery. This tear led into an intramural aortic dissection which extended posteroinferiorly to end at a point just below the origin of the renal arteries. This secondary channel was filled with clotted blood which exerted a narrowing effect upon the true aortic lumen. No point of re-entry into the true lumen was found. The renal arteries, left subclavian, left common carotid, celiac axis, and mesenteric arteries were not compromised by this dissection. There was an irregular tear on the adventitial surface of the aneurysm which measured 3 cm. in diameter and which was the point at which the dissection had ruptured into the left hemothorax—there being about 3,000 c.c. of blood in this space.

Microscopic examination of the sections from the aorta showed severe cystic medionecrosis at all levels and moderately severe atherosclerosis throughout. The dissection had occurred at the junction of the middle and outer thirds of the medial coat. The mural hematoma presented an amorphous eosinophilic appearance due to the total autolysis of the red blood cells. Reparative activity was marked about the site of the intimal rupture (Fig. 10). The fibroblasts in this area were swollen, contained pale vesicular nuclei, and showed no tendency toward an orderly orientation. It is of interest that this newly forming intimal and subintimal tissue contained many new capillaries, a most unusual observation in our experience. Furthermore, it has been demonstrated that the experimentally induced traumatic types of lesion within the rabbit aorta show no new capillaries during the phase of intimal and subintimal regeneration.[9] Organization of the intramural hematoma from the outer surface of the vessel was, however, characterized by abundant amounts of typical granulation tissue (Fig. 11). In addition to the newly formed fibroblasts and blood capillaries, there were large numbers of macrophages containing phagocytized iron and rare multinucleated giant cells.

CASE 5.—V. E. (A53-229), an 86-year-old white woman, entered Syracuse General Hospital on Nov. 21, 1947, with a chief complaint of the sudden onset of severe left chest pain that penetrated to the back and radiated to the left shoulder. Physical examination disclosed the blood pressure to be 200/110 mm. Hg and there was a weak, fast, irregular pulse. There were dullness and absent breath sounds over the base of the left lung with hyperresonance in the remainder of the lung. A few moist basilar râles were noted in the right lung. The heart was enlarged and mitral and aortic murmurs were described. The abdominal examination was negative. Roentgenograms of the chest were interpreted as being consistent with a pulmonary infarction in the left lower lobe. The patient was discharged improved.

She re-entered Syracuse General Hospital on Oct. 25, 1953, with complaints primarily related to the gastrointestinal system. Belching, flatulence, and dysphagia of several years' duration were present. No history of weight loss, diarrhea, or melena was obtained. The blood pressure at this time was 220/110 mm. Hg. Moist basilar râles and dullness

were present posteriorly over both lungs. Cardiac enlargement, aortic and mitral systolic murmurs were noted. The liver edge was stated to be 4 inches below the right costal margin in the midclavicular line. Weakness of the left leg and weak, thready pulses were present in both lower extremities. Laboratory data disclosed the hematocrit to be 21 per cent; the red blood cell count 2.2 million per cubic millimeter; white blood cell count 19,500 per c.mm., with 86 per cent polymorphonuclear leukocytes, and 14 per cent lymphocytes. Microcytosis was prominent in the smear. The urine examination was negative except for a 2+ albumin. The patient died on Oct. 26, 1953, after a steady downhill course.

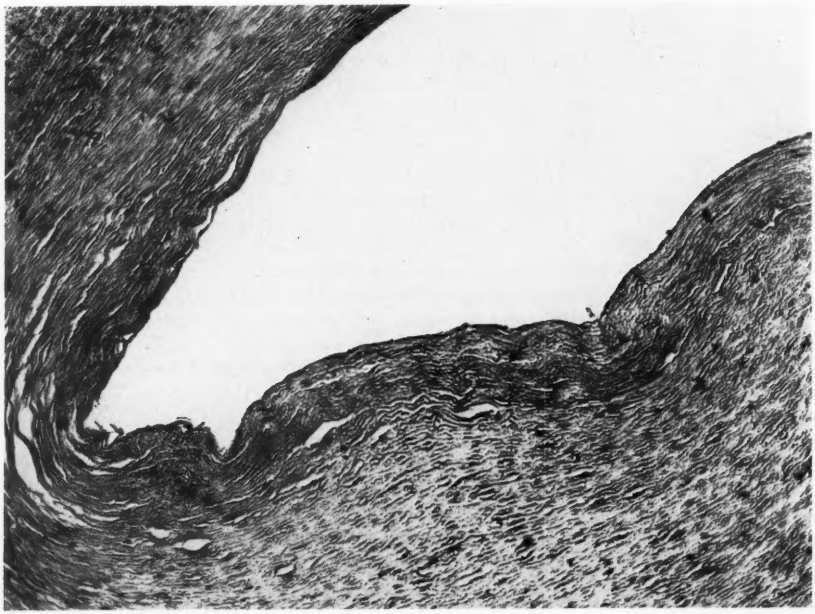

Fig. 12.—Case 5. Secondary channel showing the dense connective tissue lining. (×65.)

At autopsy the following findings were noted: adenocarcinoma of the stomach with metastasis to the liver, adenocarcinoma of the cecum arising in a sessile adenomatous polyp, pulmonary edema, and chronic pericarditis. The heart weighed 345 Gm. and showed no valvular abnormalities. Inspection of the interior of the aorta disclosed a transverse slit-like opening along the medial aspect of the midthoracic descending aorta. This opening led into a cavity within the aortic wall which was filled with cartilaginous-like material and extended 3 cm. superiorly and 3 cm. inferiorly. No other opening into this dissection was found. The greatest diameter of this aortic intramural mass was 1.5 cm. Inferiorly, just proximal to the diaphragm, a second intimal defect and intramural dissection was noted. This was also filled with cartilaginous-like material, was located on the medial wall, and measured 1.5 cm. in diameter and 7 cm. in length. The intimal slit-shaped defect was located approximately in the midportion of the dissection. Although these two intramural healed dissections were separated from each other by a distance of 1 to 2 cm., it is our impression that they were at one time contiguous and subsequently the channel became obliterated in much the same fashion as in Case 1 of the present series.

Microscopic study of the aorta disclosed severe atherosclerosis along its entire length and considerable medial calcification was also present. Cystic medionecrosis was never prominent, only rare minute foci being observed. The major portion of the blood clot within both secondary channels had been converted into a hyalinized connective tissue with considerable calcification. Both of the secondary lumens were lined by dense avascular connective tissue and well-defined endothelial cells (Fig. 12). With the use of Verhoeff's technique, very few elastic fibrils were demonstrable. It was apparent that the cleavage site in these old dissections had occurred roughly at the junction of the outer and middle thirds of the media. The vasa vasorum showed no change judged to be of significance.

DISCUSSION

A review of the literature suggests that most of the clinical and pathologic information concerning healed dissecting aneurysms is to be found in studies of reports of isolated cases.[6, 7, 10-19] Very few reviews of a large series of cases are available. The most comprehensive study of the chronic-type cases was carried out by Shennan[20] who collected 79 examples of healed aortic aneurysm from the literature. Survival for periods longer than one year was recorded in 16 of these cases. Shennan points out that re-entry of the dissection into the original lumen is a prerequisite for survival. When it did not occur, 96 per cent of the patients died within five weeks, whereas, when circulation was re-established in this way only 28 per cent died within the first five weeks. Shennan's statistics also show that if the patient survives for more than five weeks, re-entry has taken place in 90 per cent (66 of 73 cases). He pointed out that re-entry into the original lumen is particularly liable to occur when the dissection reaches some obstruction, due to increased pressure within the aneurysmal sac. The most common cause of death, in Shennan's series of chronic dissecting aneurysms, was heart failure, followed next frequently by hemorrhage from the aneurysm and cerebral hemorrhage. While the pathogenesis of the cardiac failure is not always clear, it has occurred to us that cardiac failure may often come about in a manner comparable to that associated with coaretation of the aorta, the intramural hemorrhage producing extreme narrowing of the original aortic lumen. Case 3 in our series may illustrate this type of failure since it was possible to get only the tip of the little finger into the original aortic lumen. The heart weighed 515 Gm. and the terminal blood pressure in this patient was 180/130 mm. Hg. Left ventricular hypertrophy was recorded in 65 out of 79 patients of Shennan's with healed aneurysms and he ascribed this as due either to increased work placed on the left ventricle by the new channel or due to compression of the original lumen by the new sac. Levinson and his colleagues,[16] in their study of 58 cases of dissecting aneurysm, recorded 15 patients who survived periods of from three months to eight years. They point out that this large number of cases in the chronic group is a more encouraging finding than Weiss[21] had noted in an earlier study. Weiss stated that healing occurred in about 10 per cent of all patients with dissecting aneurysm, chiefly by means of re-entry of the false passage into the true lumen at a lower level.

Considerable evidence exists to indicate that the ante-mortem diagnosis of dissecting aneurysm is being made with increased frequency.[22] While the

history and physical examination are of great importance, their value may often be restricted due to the condition of the patient. The story of excruciating epigastric or precordial pain associated with atypical patterns of radiation is strongly suggestive of dissection. Clinical evidence of shock in the presence of sustained hypertension is usually present. Paresthesias and alterations in the circulation of the extremities are not uncommon. According to Levinson[16] there is no specific electrocardiographic pattern in dissecting aneurysm, absence of electrocardiographic changes of myocardial infarction tending to support the diagnosis of aortic dissection in equivocal cases. The most useful diagnostic aid appears to be roentgenographic examination of the thorax. Intimal calcification makes measurement of the thickness of the aortic wall possible. Lodwick[23] states that the wall normally measures 2 to 3 mm. in thickness and that, while increases up to 1 cm. are suggestive, widening over 1 cm. is diagnostic of an intramural aortic hematoma. In the absence of intimal calcification, it is impossible to measure directly the thickness of the wall and the diagnosis becomes much more difficult. A widened aortic shadow may be due to elongation and stretching associated with arteriosclerosis alone, and a left-anterior oblique or right-posterior oblique view demonstrates this best according to Levene and co-workers.[24] Diffusely fusiform syphilitic aneurysms may also be confused with dissecting aneurysms on a roentgenologic basis. The margin of this type of aneurysm forms a gentle curve while in dissecting aneurysm, although the involved portion of the aorta is widened, it is of such a nature as to produce a straightening of the aortic curve in the involved segment. This straightened wall shows numerous irregularities, as in Case 3, due to larger collections of intramural blood clots at these sites (Fig. 7). The widened segment swings back to the mediastinum at an angle, and not in a curve as with the syphilitic aneurysm.

There is considerable evidence of renewed interest in the subject of dissecting aneurysm in view of the great progress of cardiovascular surgery in recent years. Surgery has been carried out in both the acute and chronic varieties of dissecting aneurysm and there is reason to believe it may have a very real role in the treatment of a condition previously considered to be hopeless. The single cases of surgical intervention reported by Gurin and collaborators,[1] Johns,[2] and by Shaw,[3] were all followed by death from renal insufficiency within the first ten days after surgery. Recently, however, DeBakey and his colleagues[4] have reported a series of 6 patients who were surgically treated, with only 2 fatalities. The duration of the dissection in this series of cases ranged from two days to thirteen months. The rationale of the surgical procedures proposed by DeBakey and his co-workers is based upon the principle that re-entry of the dissected passage at some distal point in the aorta permits restoration of peripheral circulation and removes the increasing tension upon the outer wall which predisposes to rupture. Several surgical approaches utilizing similar principles were employed. In those cases in which the dissection began in the ascending or descending arch, a re-entry passage was created into the aortic lumen with obliteration of the

false passage below. In instances in which the lesion was well localized at or below the left subclavian artery, they combined this procedure with excision of the segment involved in the origin of the dissection, followed by end-to-end anastomosis or insertion of an aortic homograft. Two important points stressed by these authors were control of hypertension, both during and following surgery, and the necessity of early intervention in the acute cases.

SUMMARY

The clinical and pathologic characteristics of 5 fatal cases of chronic (healed) dissecting aneurysms have been described. Survival time in these patients ranged from sixty-three days to several years, and the pathologic changes varied from imperfectly organized intramural hematomata to secondary endothelial-lined channels (double-barrel aortas) with abundant elastification and pronounced intimal and subintimal proliferative changes. A survey of the diagnostic measures and the surgical principles which have been utilized in cases of dissecting aneurysms has been presented.

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PNEUMOPERITONEUM AS A SPACE-OCCUPYING PROCEDURE IN CONJUNCTION WITH PULMONARY RESECTION

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THE place of lobectomy and segmental resection in the treatment of pulmonary tuberculosis is now clearly established.[1] Techniques of these procedures have been well delineated, but the problem of dealing with the residual space resulting from removal of pulmonary tissue has not been satisfactorily solved. The need for a space-filling procedure to precede, accompany, or follow pulmonary resection has concerned itself chiefly with three issues; namely, (1) conservation of pulmonary function, (2) elimination of dead space and ensuing complications resulting from failure of remaining lobes to overdistend and completely fill the hemithorax, and (3) prevention of reactivation of residual tuberculous foci.

The original idea that simple pulmonary overdistention resulted in a loss of function comparable to that produced by diffuse obstructive emphysema has now been largely discarded. On the basis of physiologic studies by Gaensler and Strieder,[2] and others,[3, 4] it has been established that postresection overdistention actually costs little in terms of impaired function of the remaining pulmonary tissue. From this standpoint alone, therefore, a space-occupying procedure hardly appears to be necessary. In fact, the commonly employed postresection thoracoplasty will usually decrease, rather than preserve pulmonary function,[2, 3] by partially collapsing the remaining lung tissue and impairing costal motion.

On the basis of these findings, a steady trend away from the use of space-occupying procedures has developed, with their selected employment only when full inflation of the remaining lung fails to occur and obliteration of dead space becomes a necessity. Chamberlain and co-workers[5] have stressed the importance of rapid elimination of all residual pleural space as a basic surgical principle if infection is to be avoided, and have stated[6] that "obliteration of the pleural dead space by complete and immediate re-expansion is the most important single factor in the postoperative management." They have indicated[6] that delayed or incomplete re-expansion will be encountered in about 6 per cent of the patients undergoing segmental resection, while Goldman and his colleagues[7] have seen this complication in 17 per cent of their patients.

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If a lobectomy or a lobectomy and resection of a superior segment is carried out, the remaining pulmonary tissue will fail to fill completely the hemithorax in an even greater number of cases.

When dead space persists, it is usually obliterated by employment of a modified thoracoplasty or some type of plombage procedure, thus requiring a second major operation. It seems logical that the incidence of residual postresection dead space might be decreased by a procedure which automatically reduces the total volume of the hemithorax before and during surgery and thus diminishes the space which the remaining pulmonary tissue must fill. If this can be accomplished without resort to multiple operations, it would appear even more desirable. As will be pointed out in subsequent discussion, artificial pneumoperitoneum seems to serve this purpose well.

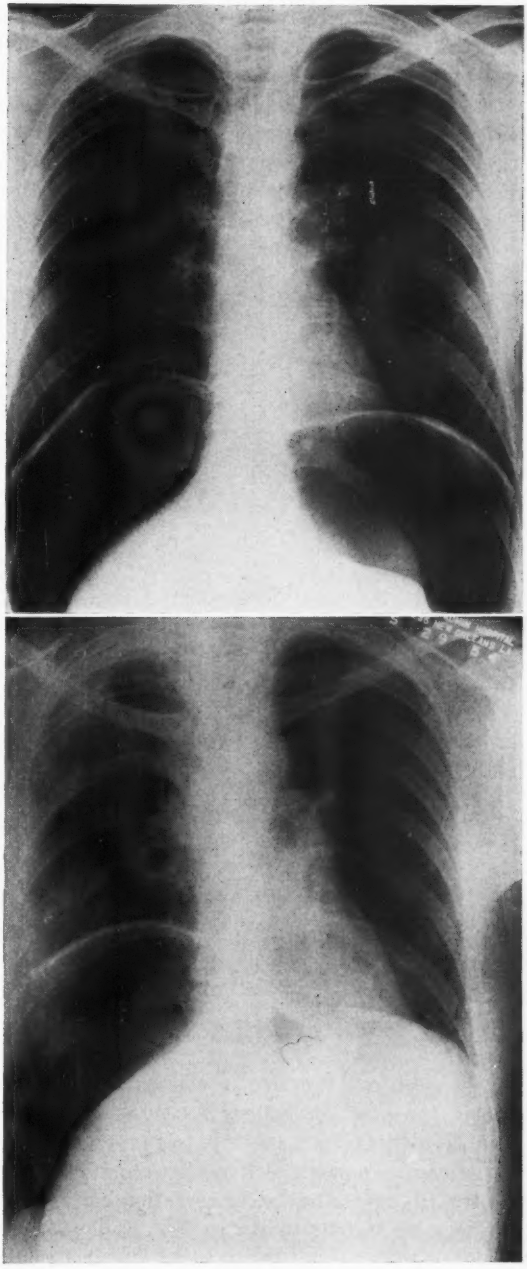
The question as to whether or not there is a significant risk of reactivation of residual disease in portions of lung which are subjected to sudden stretching, as the remaining pulmonary tissue is required to overdistend in an attempt to fill the chest, is still a controversial matter. Under the protection of specific tuberculostatic drugs the incidence of reactivated tuberculosis does not appear to be influenced by postresection hyperinflation,[3] and yet overdistention is the exact opposite of the relaxation of lung tissue produced by various collapse procedures long accepted as beneficial in promoting healing of tuberculous lesions. In any event, until further information is at hand, it would appear wise not to brush this question aside and place sole dependence on antimicrobial therapy to prevent the disaster of reactivated disease when an additional measure is available that will reduce the risk to a minimum.

The readiness with which space-filling procedures have fallen into disuse, in spite of the risks involved, is indicative that those which have been usually employed are each associated with significant disadvantages. "Partial" or "tailoring" thoracoplasty has the obvious disadvantages of producing deformity, extending the duration of the operative procedure, or requiring a second operation and reducing pulmonary function for reasons already stated.

Phrenic crush decreases pulmonary function by producing diaphragmatic paralysis and thus contributes to the development of postoperative complications.

Various plombage procedures avoid the production of thoracic deformity and probably do not cause significant further reduction of function, but require additional major surgery and are associated with important complications including fluid formation, hemorrhage, and infection.

The value of pneumoperitoneum as a space-occupying procedure in conjunction with pulmonary resection appears to have been largely overlooked. Although, Bickford and co-workers,[8] in 1951, advocated the employment of pneumoperitoneum in this way, they combined it with phrenic crush, thus adding the disadvantages of reduced pulmonary function and increased susceptibility to postoperative atelectasis. Perhaps for this reason the procedure has never attained widespread usage. Our attention was first focused on this subject by observing patients in whom pneumoperitoneum had been established as a therapeutic measure and resection carried out later. We were intrigued



A.

B.

Fig. 1.—*A*, Chest film taken four days prior to right upper lobectomy, showing moderate degree of pneumoperitoneum. *B*, Chest film taken on fourth postoperative day. Note complete redistribution of air beneath the right diaphragm producing selective elevation.

by the manner in which the air distributed itself selectively beneath the diaphragm on the operative side and reduced the size of the hemithorax. Pneumoperitoneum was thus found to function very efficiently as a space-filling procedure and presented obvious advantages. It produces no deformity, does not require additional surgery, is not associated with significant complications, causes no important reduction of pulmonary function, usually produces selective elevation of the diaphragm on the operative side, is a completely reversible procedure, and allows gradual subsequent relaxation of the remaining lung.

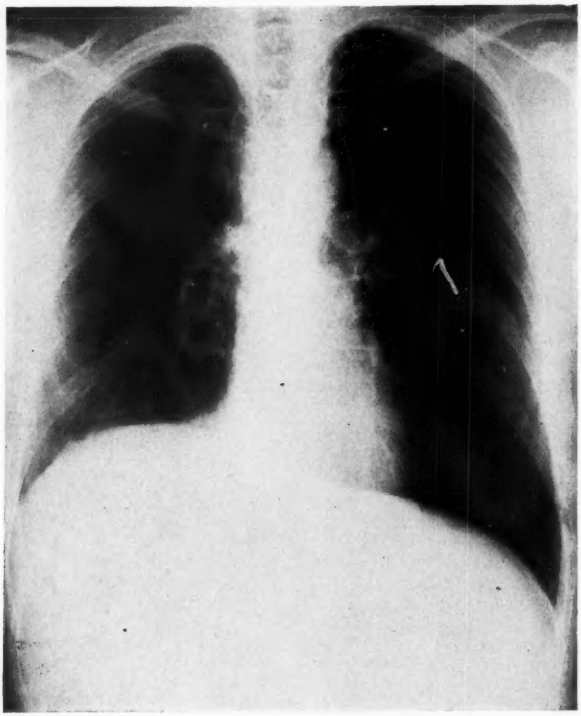


Fig. 1*C*.—Chest film taken eleven months after lobectomy. The right diaphragm remains elevated but functions well. True overdistention of the right lung has never occurred.

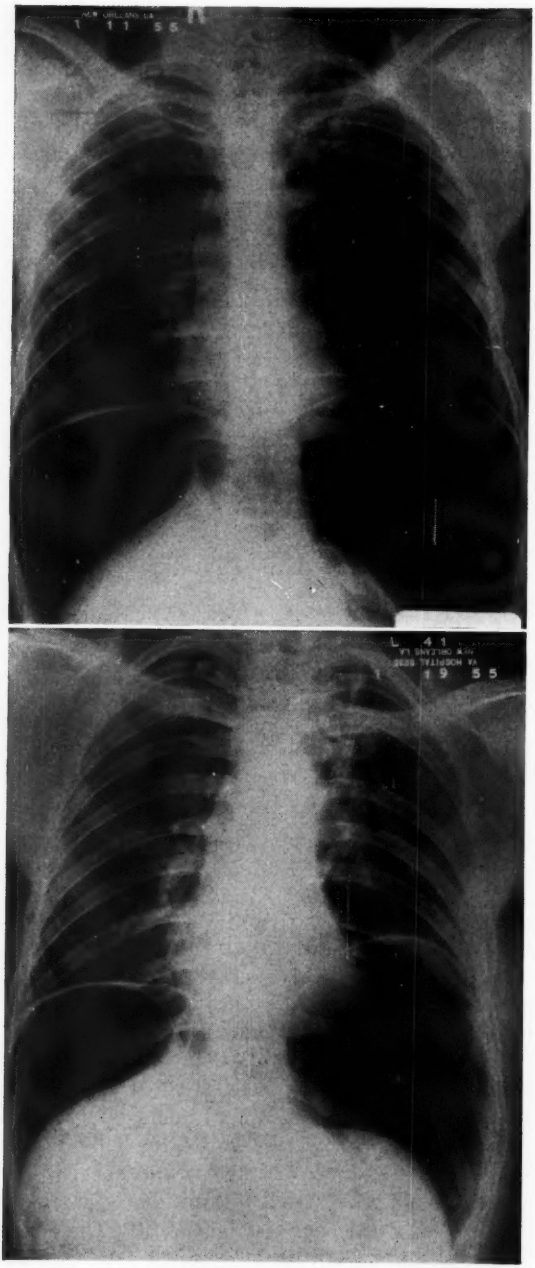
Recently, it has been our practice to employ pneumoperitoneum in conjunction with some types of pulmonary resection as a routine procedure. When it has been decided that a patient is to undergo a lobectomy or resection of multiple segments, pneumoperitoneum is induced (usually about one month prior to surgery) and a moderate elevation of the diaphragms is produced during the course of four to six refills. Following surgery, pneumoperitoneum is maintained for about two months, the first refill being given ten to fourteen days following the operation and weekly thereafter.

A total of twelve cases of lobectomy or lobectomy plus segmental resection has been managed in this fashion, and one of us (L. H. S.) has had additional experience with the procedure at another hospital. In this series, pneumoperitoneum has given excellent results. In only 1 case did the remaining lung fail to fill the hemithorax promptly and completely. This patient developed a rather intense postoperative pleural reaction and a small apical air space persisted for slightly more than two weeks before complete re-expansion was attained. No complications attributable to pneumoperitoneum have been seen, nor has there been any evidence of reactivation of residual disease. Significant complications were encountered in only 1 patient who developed postoperative atelectasis followed by a bronchopleural fistula and empyema. Another patient exhibited transient segmental atelectasis which resolved spontaneously. The manner in which the intraperitoneal air redistributes itself following surgery and produces the exact desired result is clearly illustrated in the accompanying illustrations (Figs. 1 and 2).

In an attempt to set up a comparison for the group just discussed, the last 12 patients having lobectomy or segmental resection for pulmonary tuberculosis performed at this hospital, in which neither accompanying thoracoplasty nor concomitant pneumoperitoneum was employed, were reviewed. Five of these patients had delayed re-expansion of the remaining pulmonary tissue, which in two instances required reinsertion of chest tubes and reapplication of suction. In an additional patient, re-expansion was permanently incomplete and thoracoplasty was required. One patient developed early reactivation of tuberculosis. Three patients developed significant postoperative atelectasis, and four bronchopleural fistulas were seen. Only 3 of the 12 patients were completely free of complications, although a satisfactory result was eventually attained in all cases. It seems noteworthy that 1 of the patients just mentioned, with previously induced therapeutic pneumoperitoneum, had this procedure deliberately discontinued at the time of surgery by withdrawal of air from the abdominal cavity. Interestingly enough, this patient developed atelectasis and incomplete re-expansion of the remaining pulmonary tissue.

While these two series are admittedly small, the striking difference in results appears to be significant and certainly justifies continued use of pneumoperitoneum in this fashion.

An alternate method of employing pneumoperitoneum as a space-occupying procedure on a more selective basis might be more appealing to some physicians. If, at the time of surgery, operative findings seem to indicate that the remaining lung tissue will not readily overdistend and completely fill the hemithorax, a pneumoperitoneum can be induced immediately or during the early postoperative period, thus utilizing the procedure only in selected patients. Pneumoperitoneum can be induced at the time of surgery by introducing a needle through the diaphragm from within the open chest cavity. This method, however, is mentioned only to condemn it. The danger of injury to the liver and air embolism appears to be so great that we feel this technique should never be used. A somewhat safer method involves a stab wound of



A.

B.

Fig. 2.—*A*, Chest film taken on the day prior to left upper lobectomy showing moderate degree of pneumoperitoneum. *B*, Chest film taken on seventh postoperative day. Note selective elevation of left diaphragm.

the diaphragm with the insertion of a small catheter, introduction of air beneath the diaphragm, and subsequent closure of the diaphragmatic opening by means of a purse-string suture. In spite of the advantage of selectivity offered by these methods, we do not favor introduction of pneumoperitoneum at the time of surgery or during the immediate postoperative period. We prefer the procedure now in use since it allows proper evaluation of the patient's tolerance of pneumoperitoneum and the benefits to be expected before surgery is carried out.

Fig. 2C.—Chest film taken eleven months after lobectomy. A pleurodiaphragmatic adhesion remains but the diaphragm functions well.

Some of our associates have objected to the use of pneumoperitoneum, in this manner, with claims that the presence of air in the peritoneal cavity and associated elevation of the diaphragms renders surgery technically more difficult and contributes to prolonged and irregular anesthesia. We can only state that our experiences have failed thus far to confirm these objections in a single instance.

SUMMARY

1. The value of lobectomy and segmental resection in the treatment of tuberculosis has been clearly established, but the problem of dealing with the residual space resulting from removal of pulmonary tissue continues to tax the ingenuity of the thoracic surgeon.

2. None of the commonly employed space-filling procedures have proved to be fully satisfactory, since each is associated with significant disadvantages.

3. Pneumoperitoneum appears to function very efficiently in this respect, but its value seems to have been largely overlooked. When compared to other types of space-filling methods such as thoracoplasty, plombage operations, and phrenic crush, the advantages of pneumoperitoneum become obvious. It produces no deformity, does not require additional surgery, is not associated with significant complications, causes no important reduction of pulmonary function, usually produces selective elevation of the diaphragm on the side operated upon, is a completely reversible procedure, and allows gradual subsequent relaxation of the remaining lung.

4. Although the present series is small, early favorable results certainly justify continued use of pneumoperitoneum for this purpose.

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LEIOMYOMA OF TRACHEA

Case Report

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PRIMARY benign endotracheal tumors are rare neoplasms. The successful treatment of a patient with a leiomyoma of the distal trachea which had masqueraded as bronchial asthma for three years is of sufficient interest to warrant the report of a single case.

A search of the literature revealed few endotracheal or endobronchial tumors of smooth muscle origin. Langston,[1] in a collective review of endobronchial tumors, reported two such neoplasms in the Army Institute of Pathology. Unger[2, 3] reported a tumor of the trachea which was classified as a leiomyoma. This was removed locally on several occasions by Dr. Jerome Head and later resected with the upper lobe. A plastic reconstruction was performed by suturing the bronchus intermedius to the trachea. Dr. Head[4] has also performed a pneumonectomy on another patient upon whom a lower lobe lobectomy had been performed for a papillary leiomyoma. This had extended after the initial surgery and necessitated complete removal of the lung. Following this procedure, there was tracheal involvement with eventual death from suffocation. A review of tracheal tumors by Gilbert and his colleagues[5] reported only two leiomyomas of the trachea. Hirose and Hennigar reported a case of intrabronchial leiomyoma found at autopsy; they reviewed the literature and found only two intrabronchial tumors of this type.[6] Numerous fibrous tumors are reported and, perhaps, if a careful pathologic study were made of these neoplasms, some of them would be classified as leiomyomas. Sweet and co-workers[7] pointed out the difficulty in pathologic classification of leiomyomas of the esophagus and the verification of such tumors reported in the literature. This difficulty in pathologic diagnosis is well known.

CASE REPORT

A white man, aged 56, was admitted to St. Anthony Hospital for treatment in December, 1951. The history revealed he had had onset of a nonproductive cough following a severe common cold six years prior to admission. About three years after onset, the cough became productive of mucoid sputum and there was the appearance of dyspnea. The latter seemed rather typical of asthma in that it was paroxysmal, more severe at night, and was relieved by sitting. There was expectoration of thick, tenacious, mucoid sputum. He was treated with adrenaline by inhalation and injection.

One and one-half months prior to admission, he had had a respiratory infection with fever, increased dyspnea, cough, and expectoration of purulent sputum. There had been

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Fig. 1.

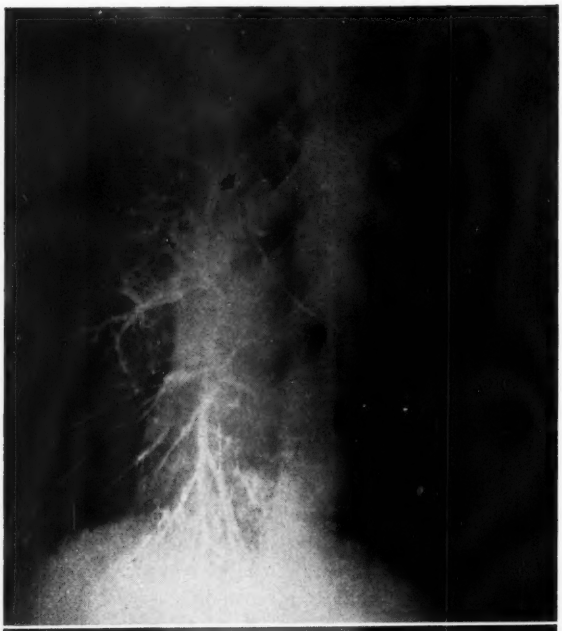

Fig. 2.

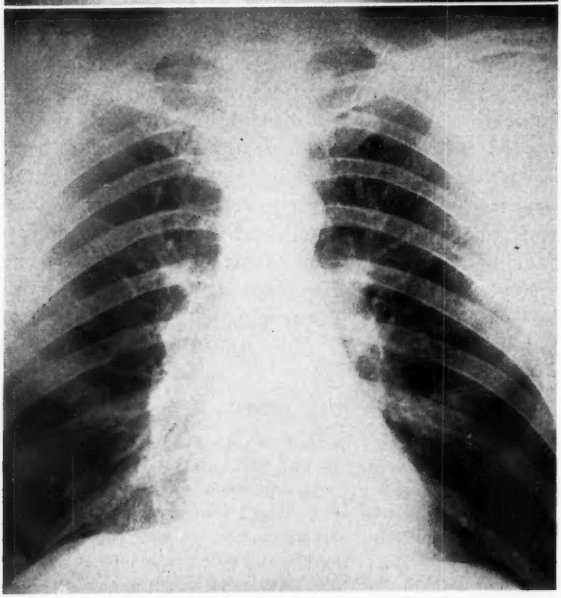

Fig. 1.—Rounded endotracheal tumor is outlined by radiopaque material in this oblique view of bronchogram.

Fig. 2.—Inspiratory posteroanterior view of chest revealed slight increase in lung markings in the right base and slight enlargement of the right hilum.

a fair response to antibiotic therapy, epinephrine, oxygen, and ACTH therapy. He was referred by his local physician, because it was felt there was a suppurative process or some other pathologic condition underlying the asthma.

The past history revealed that he had had a bronchogram made three years prior to the admission and it was said to have shown some bronchiectasis of the right lower lobe (Fig. 1). A review of these bronchograms showed the tumor well demonstrated; however, these were not obtained until after treatment had been carried out.

Examination of the patient revealed moderate respiratory distress, both inspiratory and expiratory, but chiefly the latter. Dry sibilant râles were heard bilaterally without any localizing signs. There was much mucoid sputum raised which seemed to give temporary relief.

Roentgenograms of the chest and fluoroscopy revealed the lung markings to be increased in the right base posteriorly, and some thickening of the right hilum with apparent pulsation upon fluoroscopy which was thought to be the pulmonary artery. Inspiration and expiration films were of no aid (Fig. 2).

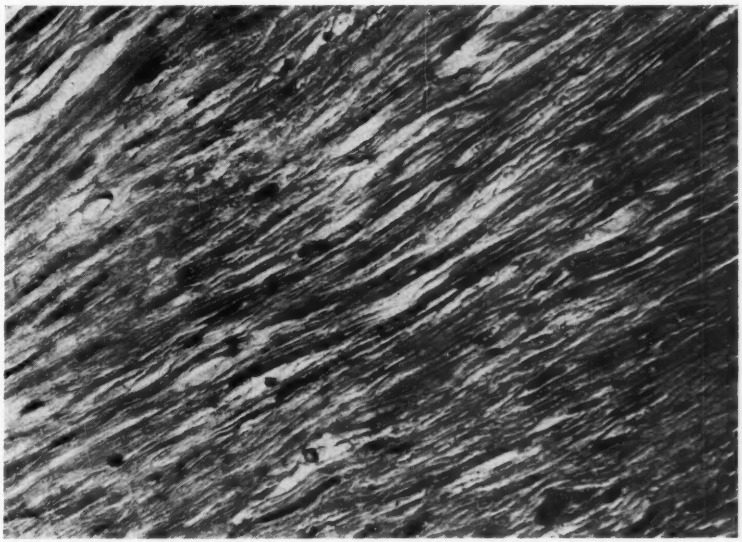

Fig. 3.—Photomicrograph demonstrates the well-differentiated smooth muscle cells arranged in bundles with a whirled appearance. Some of the nuclei appear large, but no mitotic figures were seen.

The patient responded to epinephrine, sedation, oxygen, potassium iodide, and intravenous glucose therapy, and was discharged to be followed by the allergist. He failed to continue to do well on these measures, however. There were repeated milder attacks of dyspnea, and the cough persisted even when there was no dyspnea. He was admitted again to the hospital on Jan. 6, 1953.

Bronchoscopy revealed a pink, smooth, slightly lobulated tumor in the distal trachea, almost occluding the entire lumen at the bifurcation. There was only a small air passage to both main-stem bronchi anterior to the tumor. The biopsy was reported as demonstrating a benign tumor. Piecemeal removal of the tumor was attempted through the bronchoscope, and about one third of the tumor was removed in this fashion. There was

moderate bleeding with this manipulation, and more could not be done at this time because of the firm nature of the tumor. However, an airway was established along the left side, and it was then evident that the tumor arose from the membranous portion of the trachea in an area about 1.5 cm. in diameter.

About fourteen hours later, the patient had a severe attack of dyspnea, cyanosis, and loss of consciousness for a few seconds. Moderate dyspnea continued, the cause of which was not apparent. When a bronchoscope was introduced, there appeared to be a larger airway present than prior to the piecemeal removal. Enough tumor had probably been removed to allow the remainder to rotate upward into the trachea and thus occlude more airway than in its former position when confined to the bifurcation.

A long endotracheal tube was passed into the left bronchus, and a right thoracotomy was performed under general anesthesia. The tumor was removed by a longitudinal incision in the membranous portion of the trachea and right main-stem bronchus. The mass was delivered and removed with the mucosa. The wall was closed with interrupted sutures of No. 3-0 black silk and no air leak was evident with positive pressure. The chest was closed in the usual fashion with two thoracotomy tubes. A tracheotomy was performed at the termination of the operation.

Convalescence was uneventful, and there have been no subsequent asthmatic symptoms. Bronchoscopy, performed three months postoperatively, revealed no abnormality of the trachea and no evidence of the previous surgery. He is asymptomatic three and one-half years following surgery.

The tumor was comprised of well-differentiated, smooth muscle cells, arranged in bundles, which had a whirled appearance. Some of the nuclei were large; however, no mitotic figures were seen. In most areas the nuclei were separated by the fibers of the smooth muscles, which produced a dense rather than cellular appearance. Portions were covered by respiratory epithelium and there were some areas of squamous-cell metaplasia. A Weigert-Van Gieson stain showed most of the tissue to be stained yellow (smooth muscle). A few small strands of red-stained tissue were present throughout the section (connective tissue) (Fig. 3).

Sections were sent to Dr. J. B. Hazard, Cleveland Clinic Foundation, Cleveland, Ohio, and he was in agreement with the diagnosis of leiomyoma of the trachea.

DISCUSSION

The symptom of cough, which preceded by two years the onset of wheezing and dyspnea, and persisted, despite periods of relief, pointed to the necessity of a diagnostic bronchoscopy. Clagett, Moersch, and Grindlay[8] have emphasized that recent onset of wheezing in a patient more than 40 years of age should not be considered to be due to bronchial asthma until the possible presence of an obstructing lesion of the trachea has been excluded. The symptoms are dependent upon the obstructing nature of the lesion, ulceration, and secondary infection. Cough is a common symptom and very often is dry or productive of mucoid sputum. At times the sputum is purulent due to secondary infection or blood streaked secondary to ulceration. Dyspnea and wheezing are rather constant symptoms and may be intermittent or constant. These two latter symptoms frequently lead to a mistaken diagnosis of asthma for obstructing lesions of the trachea.

Endotracheal tumor may be evident by roentgenologic study but absolute diagnosis is dependent upon bronchoscopy and tissue study. Special x-rays such as a lateral view of the trachea or overexposed posteroanterior films may demonstrate an opaque lesion in the air-filled air passages. Often tumors

arising in the trachea are not visualized at all upon routine posteroanterior views, as is well demonstrated by this reported case. Bronchography may be a valuable adjunct because the tumor mass may show readily with this double contrast technique. Planigrams and Bucky films are helpful but were not used in this instance.

Treatment consists of removal of the tumor, either by endoscopic piecemeal removal or by tracheotomy. In the reported case, the firm nature of the tissue precluded removal of sufficient amount to be safe, and second, because the rather wide base of origin from the mucosa was not visible due to the size of the tumor, it was not possible to attack this area of origin directly. A resectoscope may be useful in these instances.

Bronchoscopy or tracheotomy through the membranous portion of the bronchus or trachea is easily performed and was the method chosen, as sufficient tissue could not be removed piecemeal without danger of a respiratory accident. In case of either benign or malignant intrathoracic tracheal tumors, where the entire thickness of the tracheal wall may be involved and must be removed, plastic repair is possible as evidenced by successful cases reported by Clagett, Moersch and Grindlay,[8] and repair of stenotic lesions reported by Gebauer.[9]

SUMMARY

An endotracheal leiomyoma caused symptoms suggesting asthma. The diagnosis of tumor of the distal trachea was made by bronchoscopy and removal was performed by thoracotomy and tracheotomy.

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THE ANATOMY OF THE BRONCHIAL ARTERIES OF THE DOG

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THE importance of the bronchial arteries in the pulmonary blood circulation has been repeatedly observed since they were first described by Ruysch[1] and Haller[2]; likewise their participation in various vascular and parenchymatous pathologic processes of the lungs has been noted, whether these be of natural origin or experimentally produced. The subject has been well reviewed by Cauldwell,[3] Liebow[4] and their colleagues, and Tobin and Zariquiey.[5]

Where knowledge concerning the bronchial arteries has been gained from experimental procedures, these experiments have usually been carried out on the other vessels of the lung, the effects upon the bronchial arteries or the responses on their part being thereafter observed. Very few experiments have been based upon direct operative intervention on the bronchial arteries. This is mainly due to technical difficulties which result from their small caliber, and the great number of branches that enter the lung, as well as from their rich anastomoses and intimate relations with the other structures of the pulmonary pedicle. Thus, Mathes and his co-workers,[6] after trying to ligate the bronchial arteries of the dog, wrote as follows, "The isolation and ligation of the entire bronchial arteries was found to be impossible after several attempts. The main arteries arising from the aorta were tied, but in each case after autopsy the lung was entirely normal and the bronchial artery injected in its entirety from the bronchial vessels arising from the intercostal artery." More recently Tobin and Zariquiey[5] have stated, "The tortuous course and the location of the bronchial arteries, however, make it almost a physical impossibility to occlude them directly without closure of the bronchial lumen."

The present work was undertaken to acquire a more exact knowledge of the topographical anatomy of the bronchial arteries of the dog, particularly as regards their origin and their mediastinal course; it was considered that such knowledge might well facilitate operative procedures upon these vessels.

Although complete and detailed descriptions of the topographical anatomy of the bronchial arteries in man have been made by several authors,[3, 7, 8] the topographical anatomy of the bronchial arteries in the dog has been inadequately dealt with. Detailed descriptions are lacking from current literature, as well as from texts on the anatomy of the dog.

Küttner[9] described the bronchial arteries of the dog as follows: "*The posterior bronchial artery* arises by a common trunk with the intercostal artery

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at the level of the 6th thoracic vertebra; it divides into right and left branches, the right one supplying branches to the oesophagus. A posterior bronchial artery arising from the 1st intercostal artery is very rarely found. *The anterior bronchial arteries* arise in part from the internal mammary artery, in part from the descending tracheal artery. Smaller branches come from the pericardial arteries and make their way into the pulmonary hilus together with mediastinal and tracheo-oesophageal arteries."

A similar description has been given by Berry and his colleagues,[10] who also describe anterior and posterior bronchial arteries. They add that the posterior bronchial artery to the right lung may arise directly from the thoracic aorta and that to the left lung from the left sixth intercostal artery. They emphasize that the posterior bronchial arteries are much larger than the anterior.

Mathes and his co-workers[6] have given a somewhat different account as follows, "It arises in one to three trunks from the anterior side of the descending aorta, just distal to the aortic arch. Frequent variations in its origin are met with; the artery on the right commonly arises from the first intercostal artery, and occasionally from the internal mammary or subclavian artery."

Bradley[11] describes bronchial branches to the superior pulmonary lobe originating from the internal mammary artery, and two or three small bronchial arteries arising either directly from the aorta or from its first intercostal branch; these latter bronchial arteries supply also the bronchial lymph nodes and the esophagus.

Miller[12] describes the bronchial arteries in the following manner, "The oesophageal and bronchial arteries vary in number and origin. Usually, the chief supply to the lungs is an artery which leaves the right sixth (rarely seventh) intercostal artery, close to its origin. This is the small *'bronco oesophageal artery.'* It crosses the left face of the oesophagus and contributes a branch to it, the oesophageal artery. It terminates shortly afterwards in right and left bronchial arteries which supply the lymph nodes and the connective tissue of the root of the lungs. The oesophagus always receives branches from some of the right intercostal arteries, caudal to the sixth. The lungs frequently receive additional branches from adjacent intercostals also."

Bourdelle and Bressou[13] state that "a bronchial artery" arises from the thoracic aorta and proceeds from there to the bifurcation of the trachea to be distributed in the lung.

MATERIALS AND METHODS

The present work is based on the dissection of 30 dogs, male and female, of different breeds and of various ages. The bronchial arteries of these dogs were filled with colored latex; injection of the latex, in some instances, was made into the femoral or common carotid artery and in others directly into the aorta or one of its branches. In some cases, the thorax was opened prior to injection so that the lungs retracted; in other cases, the thorax remained closed. No difference in the filling of the arteries was observed in using these

two methods nor did artificial inflation of the lungs via the trachea affect the filling. In those cases where the thorax was already open at the time of injection, the aorta was ligated at its exit from the heart so as to prevent the injection material from flowing backward into the pulmonary veins.

The latex injections were made either with a veterinary syringe having a rubber piston or by means of an air-compressor like that used for tree-spraying. The compressor, with its manometer, is connected by rubber-tubing to a flask containing the latex; a second tube emerging from the flask is connected to the injection needle. This apparatus proved to be most practical.

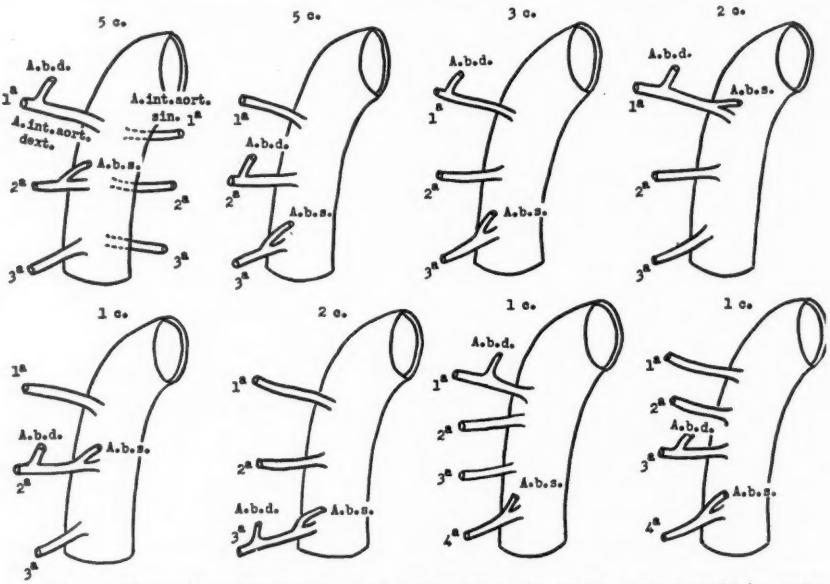

Fig. 1.—Schematic representation of the variations in the origins of the bronchial arteries from the aortic intercostal arteries.

Type I.—(66.6 per cent). One right and one left bronchial artery.
A.int.aort.dext.: Arteria intercostalis aortica dextra.
A.int.aort.sin.: Arteria intercostalis aortica sinistra.
A.b.d.cran.: Arteria bronchialis dextra cranialis.
A.b.s.cran.: Arteria bronchialis sinistra cranialis.
A.b.d.caud.: Arteria bronchialis dextra caudalis.
A.b.s.caud.: Arteria bronchialis sinistra caudalis.
1 c. to 5 c. represent the number of cases observed.

After fixation of the parts in formalin for a few days, the sternum in each case was removed and also the greater part of the ribs to within a few centimeters of the vertebral column. On drawing the lungs ventrally, the ramifications of the injected bronchial arteries were clearly observed through the transparent parietal pleura and were then dissected toward their origins and terminations.

OBSERVATIONS AND DESCRIPTION

One or two bronchial arteries were found going to each lung. Where two arteries are present on one side they are referred to in the present paper as the cranial and caudal bronchial arteries (right or left), respectively.

For convenience the cases were grouped as follows (Table I):

Type I: 1 right and 1 left bronchial artery
Type II: 1 right and 2 left bronchial arteries
Type III: 2 right and 1 left bronchial artery
Type IV: 2 right and 2 left bronchial arteries.

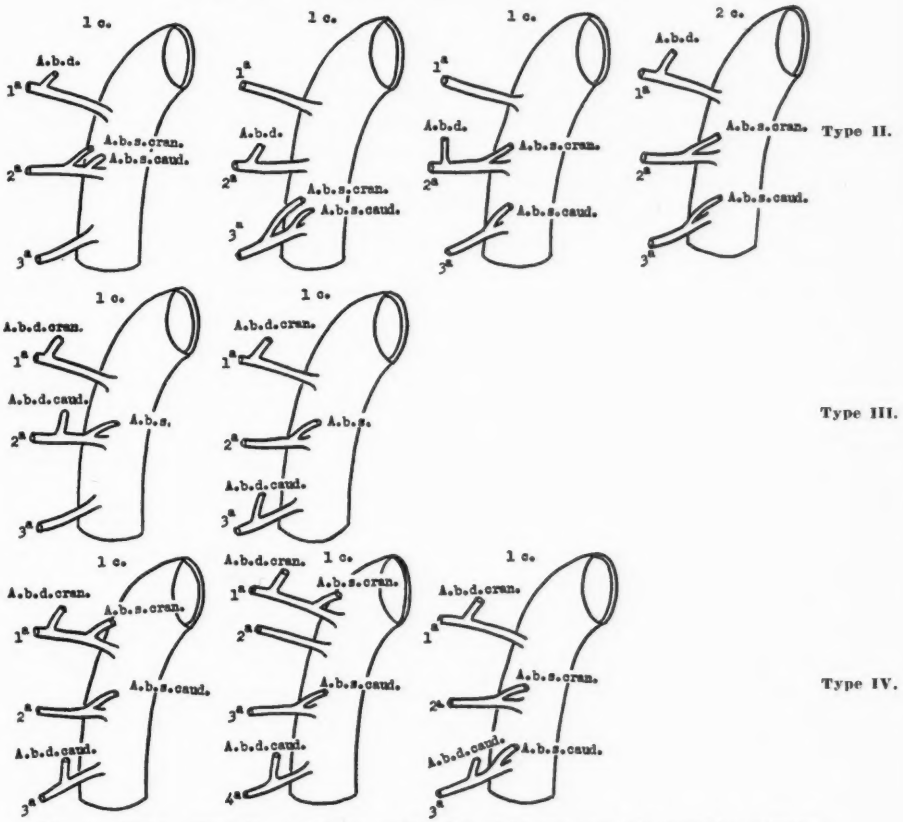

Fig. 1.—Cont'd. Type II. (16.6 per cent). One right and two left bronchial arteries.
Type III. (6.6 per cent). Two right and one left bronchial arteries.
Type IV. (10 per cent). Two right and two left bronchial arteries.

Fig. 1 shows schematically all the possible variations of origin and the frequency with which they were met. It will be seen that Type I was by far the most common.

TABLE I. CLASSIFICATION OF CASES ACCORDING TO NUMBER OF BRONCHIAL ARTERIES OF AORTIC INTERCOSTAL ORIGIN TO EACH SIDE

TYPE	BRONCHIAL ARTERY		NUMBER OF CASES	PER CENT
	RIGHT	LEFT		
I	1	1	20	66.6
II	1	2	5	16.6
III	2	1	2	6.6
IV	2	2	3	10.0

Origin.—

The bronchial arteries of *both* sides were found to arise from the *right* aortic intercostal arteries. In no case were they found arising directly from the aorta or from the left intercostal arteries.

The point of origin from the intercostal arteries differs according to the bronchial artery in question; it was found at a distance of 0.5 mm. to 25 mm. from the aorta.

The right bronchial arteries generally arise from the intercostal arteries considerably farther from the aorta than the left ones; the cranial bronchial arteries arise farther away from the aorta than the caudal ones. Thus, the right cranial artery arises farthest from the aorta, and the left caudal rises nearest the aorta (Fig. 1). When the point of origin of a bronchial artery is very close to the aorta, that is, when there is a very short common trunk of origin from the bronchial and intercostal arteries (i.e., a very short "intercostobronchial artery"[3]), it may at first sight appear that the bronchial artery arises directly from the aorta, but by close observation its origin from the intercostal artery may be distinguished. This often happens with the left caudal bronchial artery.

The particular right *aortic* intercostal arteries from which a bronchial artery may spring are the first to the fourth. The frequency with which the different bronchial arteries arise from these intercostal arteries is shown in Table II, where it may be seen that most right bronchial arteries arise from the first or second aortic intercostal arteries, while the left bronchial arteries arise most commonly from the second or third aortic intercostal.

TABLE II. FREQUENCY OF ORIGINS OF BRONCHIAL ARTERIES FROM AORTIC INTERCOSTAL ARTERIES

RIGHT AORTIC INTERCOSTAL ARTERY	RIGHT BRONCHIAL ARTERIES			LEFT BRONCHIAL ARTERIES			TOTAL
	SINGLE	DOUBLE		SINGLE	DOUBLE		
		CRANIAL	CAUDAL		CRANIAL	CAUDAL	
First	14	5	–	2	2	–	23
Second	8	–	1	8	5	2	24
Third	3	–	3	10	1	6	23
Fourth	–	–	1	2	–	–	3

It is to be noted that the numbering of the aortic intercostal arteries does not correspond to that of the intercostal spaces. A variable number (1 to 4) upper intercostal spaces are supplied by the costocervical trunk of the subclavian artery. The aortic intercostal arteries from which the bronchial arteries arise (i.e., first to fourth) pass to the third to eighth intercostal spaces; one aortic intercostal artery may supply more than one intercostal space.

It is convenient also to relate the points of origin of the bronchial arteries (from the intercostal arteries) to vertebral levels. Because of the oblique course taken by the intercostal arteries, they, i.e., the intercostal arteries, may arise from the aorta at a level higher or lower than the inter-

costal spaces to which they are distributed (Fig. 2). Thus, it may be noted from Table III that the vertebral levels of the points of origin of the bronchial arteries extend from the disc between the fourth and the fifth thoracic vertebra down to the eighth thoracic vertebra. The majority of the right bronchial arteries have their origin in front of the fifth and sixth thoracic vertebrae and the disc between them, while most left bronchial arteries arise in front of the sixth and seventh thoracic vertebrae and the disc between them.

TABLE III. VERTEBRAL LEVEL OF ORIGIN OF THE BRONCHIAL ARTERIES FROM THE AORTIC INTERCOSTAL ARTERIES

VERTEBRAL LEVEL	RIGHT BRONCHIAL ARTERY			LEFT BRONCHIAL ARTERY			TOTAL
	SINGLE	DOUBLE		SINGLE	DOUBLE		
		CRANIAL	CAUDAL		CRANIAL	CAUDAL	
T_4	-	-	-	-	-	-	-
Disc T_4-T_5	2	-	-	-	1	-	3
T_5	7	2	-	2	1	1	13
Disc T_5-T_6	6	2	-	2	1	1	12
T_6	9	1	3	10	4	2	29
Disc T_6-T_7	-	-	-	1	1	1	3
T_7	1	-	1	7	-	3	12
Disc T_7-T_8	-	-	-	-	-	-	-
T_8	-	-	1	-	-	-	1

Disc = Intervertebral disc.
T = Thoracic vertebra.

The aortic intercostal arteries, giving origin to the bronchial arteries, spring from the right lateral aspect of the descending aorta, sometimes close to its ventral aspect or even from the right lateral portion of the ventral aspect itself. Very often these intercostals have a greater caliber than the remaining intercostal arteries.

Course (Figs. 1-4).—

Right bronchial arteries:

A. Single right bronchial artery: This is the most constant of the bronchial arteries in its origin, course, and distribution. It springs from the first, second, or third right intercostal artery 10 to 25 mm. from the aorta, it passes upward and forward, lying first on the right side of the vertebral column, then, crossing the right aspect of the esophagus, it reaches the trachea, descends upon the right main bronchus and divides into its various branches which enter the lung with that bronchus. At the level of the trachea, the right bronchial artery crosses the vagus nerve on its lateral side or it intermingles with the various branches into which the vagus nerve has divided at that level. On the whole, the artery describes an arch open downward and

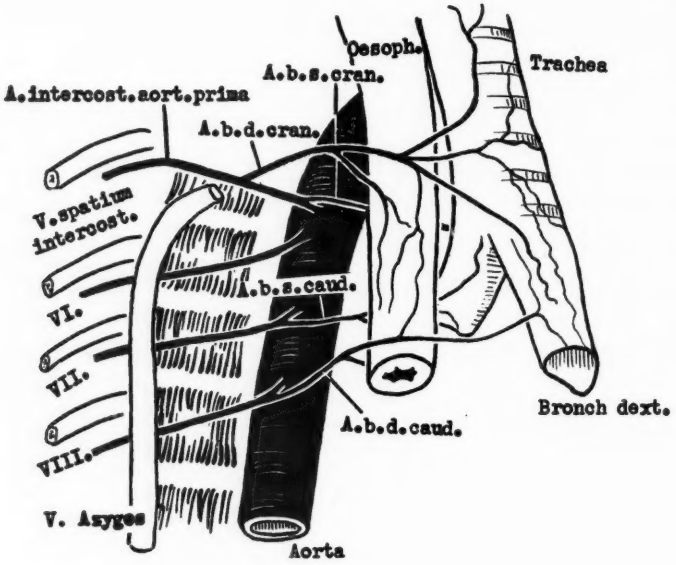

Fig. 2.

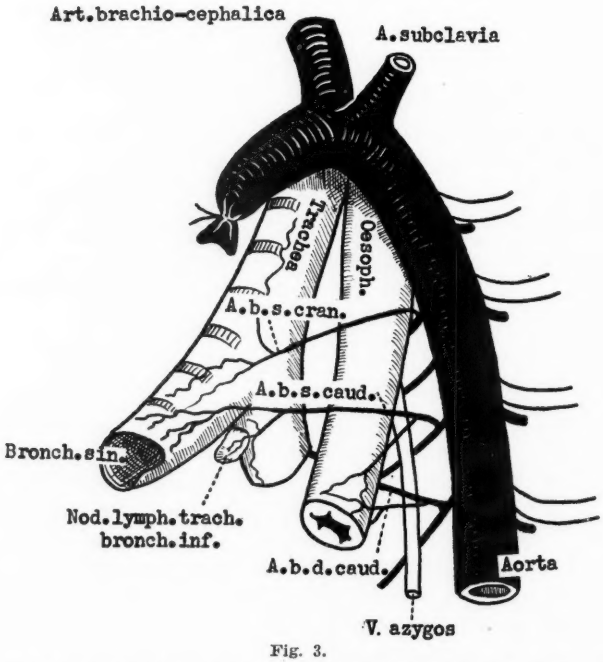

Fig. 3.

Figs. 2 and 3.—Origins and course of bronchial arteries as seen from the right (Fig. 2) and from the left (Fig. 3) in a Type IV case. In cases where a single artery only is present on one or the other side, its course is represented by the cranial of the two bronchial arteries shown in these figures. (For key to lettering see legend to Fig. 1.)

backward. In the first part of its course it runs nearly parallel to the arch of the azygos vein which may partially overlap the artery; in only 2 cases (6.6 per cent) was the artery seen to cross the lateral aspect of the azygos vein.

B. Double right bronchial arteries: 1. Where two right bronchial arteries are found, the cranial of the two, here called the *right cranial bronchial artery,* corresponds to the single right bronchial artery in its course and relations as described previously. It usually arises from the first intercostal artery.

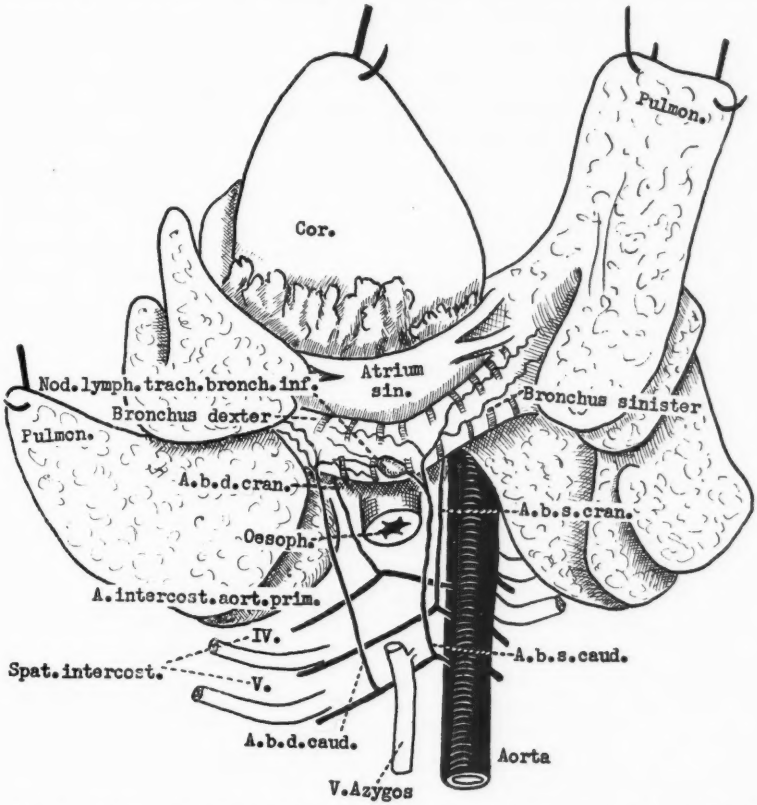

Fig. 4.—Origins and course of bronchial arteries (Type IV) as seen from the front. The heart has been drawn upward and the lungs drawn aside. The bifurcation of the trachea is thus shown. The esophagus and the azygos vein have been cut.

Nod.lymph.trach.bronch.inf.: Noduli lymphatici tracheo-bronchiales inferiori.

Spat.intercost.: Spatium intercostale.

(For key to remaining lettering see legend to Fig. 1.)

2. *The right caudal bronchial artery* was seen to arise from the second, third, or fourth right aortic intercostal artery, 3 to 12 mm. from the aorta. It runs upward and forward, its direction being more vertical, the lower its point of origin. It crosses the right aspect of the esophagus and reaches the posterior aspect of the right main bronchus, with which it descends, dividing into its various branches.

In some cases, small branches from one or both of the right bronchial arteries were seen to reach the left main bronchus, either directly or by crossing the inferior tracheobronchial lymphatic glands. (It will be pointed out later that, more frequently, the right main bronchus, in a similar way, receives branches from the left bronchial arteries.)

Left bronchial arteries:

A. Single left bronchial artery: This is more inconstant in its course and relations than the right arteries. It arises from the first, second, or third right aortic intercostal artery, generally from the second or third (Table II), at a distance of 0.5 to 5 mm. from the aorta. It first passes to the left, between the aorta and the esophagus, then, crossing the left aspect of the latter, it reaches the left main bronchus or it may first pass on to the trachea and then descend to the bronchus, having already divided into its branches. It crosses the left vagus nerve on its medial side or it is intermingled with the ramifications of the nerve.

B. Double left bronchial arteries: 1. Where two bronchial arteries are present the cranial of the two, here called the *left cranial bronchial artery,* is similar in its origin, course, and relations to the single left bronchial artery. It arises rather constantly from the second right aortic intercostal artery (Table II, Fig. 1). 2. The *left caudal bronchial artery* arises from the second or third right aortic intercostal artery, 0.5 mm. to 3 mm. from the aorta. Its course and relations are similar to those of the left superior artery, but it reaches the left main bronchus at a lower level.

Frequently the left bronchial arteries give off branches which supply the inferior tracheobronchial lymph glands and these branches continue on to the *right* main bronchus; small branches passing directly to the right bronchi were observed as well (see Figs. 3 and 4). As already noted, in a similar way, though less frequently, the right bronchial arteries give off branches to the left main bronchus. Branches of this kind are generally small and end in the proximal part of the main bronchus, but sometimes they are important and descend together with the ipsilateral bronchial arteries. In some of these cases it is justifiable to consider the bronchial arteries to the two main bronchi as arising by a common stem which ends by dividing into terminal branches for both main bronchi. Thus, the lungs may receive blood supplied to them by the bronchial arteries of both sides.

Branches.—

Throughout their mediastinal course, the bronchial arteries give off branches to organs and tissues in the neighborhood. The name "bronchomediastinal arteries" would fit them better because of their distribution.

Among the branches of the bronchial arteries are the following:

1. *Parietal branches:* to the prevertebral muscles and the vertebrae.
2. *Pleural branches:* to the mediastinal pleura, to the pleura of the root of the lung and to the most proximal part of the visceral pleura.
3. *Esophageal branches:* to the thoracic portion of the esophagus.

4. *Tracheal branches:* to the inferior portion of the trachea.

5. *Branches to nerves:* a. To the vagi: each bronchial artery gives off branches to the nerve of the corresponding side; these branches ascend and descend with the nerve. There are twigs accompanying the branches of the nerves to the pulmonary plexus, and on the left side branches ascend with the left recurrent laryngeal nerve. b. Inconstant branches to the sympathetic trunk, its ganglia and branches.

6. *Pericardial branches:* small branches to the nearby pericardium.

7. *Vasa vasorum:* from the right bronchial arteries, especially to the azygos vein and the superior vena cava; from the left bronchial arteries to the aortic arch and descending aorta. Both right and left bronchial arteries give branches to the ipsilateral pulmonary arteries and veins.

8. *Branches to lymph glands:* the lymph glands of the pulmonary pedicle and the superior tracheobronchial glands receive branches from the bronchial arteries of the corresponding side. The inferior tracheobronchial glands (i.e., glands of the tracheal bifurcation) may receive their supply from both sides or mainly from one of the bronchial arteries. As has been pointed out already, it can often be observed that these glands are sometimes pierced by branches of the bronchial arteries which pass to the opposite side.

Anastomoses.—

Frequent and rich anastomoses are observed between the branches of the artery of the same side, both before and after they reach the main bronchus; at the level of the tracheal bifurcation and among the inferior tracheobronchial lymph glands, one may observe fine anastomoses between the arteries of the two sides. Furthermore, by means of the branches from the bronchial arteries to the various mediastinal organs and the parietes, rich anastomoses are built up between the bronchial arteries and the arteries supplying those regions, e.g., innominate or brachiocephalic, subclavian, internal mammary, inferior thyroid, intercostal, thymic, diaphragmatic, and pericardial arteries. In certain cases, some anastomoses attain considerable proportions, so that the impression is created that the bronchial branches are continuations of those anastomoses; this can be observed especially on the trachea and the esophagus.

Other Bronchial Arteries to the Lungs.—

In one case (Type II), the right pericardiophrenic artery was seen to give branches to the right bronchus.

In one other case (Type I), a thin branch from the sixth right aortic intercostal artery which passed to the tenth intercostal space reached the inferior lobe of the lung via the pulmonary ligament.

DISCUSSION AND CONCLUSIONS

A striking feature of the anatomy of the bronchial arteries is the asymmetry of their origin; these arteries supply bilateral organs, more or less symmetrical, yet they arise, in the main, from the intercostal arteries of the right side. Such a tendency is already observed in man,[3] where the bronchial

arteries spring either directly from the aorta (generally from the most right part of its anterior aspect), or from the right intercostal arteries, but never from the left intercostal arteries. It must be in very rare cases only that a bronchial artery arises from a left intercostal artery as described for the dog by Berry and his co-workers.[10] Caldwell and his colleagues[3] describe such an origin in man only in cases of situs inversus. With regard to the descriptions by others[6, 10, 11, 13] of bronchial arteries in the dog arising directly from the aorta, it is my impression that arteries which appear to arise in this manner do not in fact do so, but arise from an aortic intercostal artery close to its point of origin from the aorta.

Earlier workers[9, 10] have classified the bronchial arteries into anterior and posterior groups, the former arising from the internal mammary and its branches or from other arteries in the vicinity. In the present study, the arteries found to arise from intercostal arteries correspond with the posterior group named by these authors and they constitute the constant and most important systemic arterial supply to the lungs. As far as the anterior group is concerned, these were found in general to be small and inconstant and always merely accessory to the main supply from the posterior group.

Regarding the description of Küttner[9] and Miller,[12] that the supply to the right and left bronchi arises by a common trunk which subsequently divides to supply both sides, it was always found in the present work that separate bronchial arteries to each side were present, arising independently from aortic intercostal arteries. Frequently, however, one or another of these bronchial arteries gives branches to both sides.

As a practical application of the present anatomic description, it can be seen that the best approach to the bronchial arteries of *both* lungs in the dog is from the right side. Thus, the right hemithorax is opened and the lung drawn ventrally. On separating the esophagus from the aorta, the origin of the bronchial arteries *for both sides* may easily be localized by following the first four *aortic* intercostal arteries. The only element that overlaps the right bronchial arteries in addition to the parietal pleura is the arch of the azygos vein.

The present study contains the results of observations made on a limited number of dissections, and shows therefore only the most frequent variations in the anatomy of the bronchial arteries. It is possible that there are variations other than those just described. Thus, apart from arteries entering the lung by way of its hilum or the pulmonary ligament, branches entering any part of its surface through pleural adhesions (either naturally or experimentally produced) have been described. Furthermore, arteries of completely anomalous origin and course have been described as sometimes arising in the abdomen and perforating the diaphragm on their way to the thorax.[14]

All these possibilities of arterial blood supply, as well as the numerous and various anastomoses of the bronchial arteries with the arteries of neighboring organs, must be taken into account in a study of the systemic bronchopulmonary circulation.

SUMMARY

In dissections made on 30 dogs, whose arteries were previously injected with latex, one or two bronchial arteries were observed on each side. It was possible to group the cases into 4 principal types.

Type I: 1 right and 1 left bronchial artery (66.6%)
Type II: 1 right and 2 left bronchial arteries (16.6%)
Type III: 2 right and 1 left bronchial artery (6.6%)
Type IV: 2 right and 2 left bronchial arteries (10.0%)

The bronchial arteries were found in all cases to spring from the first to the fourth right aortic intercostal arteries. They were never seen to arise directly from the aorta or from the left intercostal arteries. Their vertebral level of origin extends from the disc between the fourth and fifth thoracic vertebrae down to the eighth thoracic vertebra. The course, relations, distribution, and anastomoses of the arteries are described and the best method of approach to them is outlined. Other possible sources of systemic arterial supply to the lungs are pointed out.

I am deeply indebted to Mr. Zvi Lev of the Pedagogical Institute for Science, Jerusalem, for invaluable help rendered throughout the entire course of this work. My thanks are also due to Prof. M. Ickowicz and Dr. G. Gitlin for assistance in revision of the manuscript, to Mrs. E. Salomon for the drawings, and to Mr. Isaac Hayoun for technical assistance.

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PRIMARY LYMPHOSARCOMA OF THE LUNG

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PRIMARY lymphosarcoma of the lung is a rare lesion. Only 21 cases have been previously reported. A summary of the literature and 2 additional cases will be presented.

CLINICAL DATA

Including our 2 cases, there are 16 cases in which clinical details are recorded (Table I). Of these 16 patients, there are 7 who had symptoms. Average duration of symptoms previous to operation was twelve months. Cough was present in 4, hemoptysis in 2, weight loss in 2, malaise and easy fatigability in 3, and mild chest or shoulder pain in 3 patients. Since the lesion is a consolidation usually without bronchial obstruction, the physical findings when present are those of consolidation. The x-ray findings are consistent with the morphology and are in no way diagnostic.

Thirteen of the patients were bronchoscoped. In 5, bronchial compression, edematous and granular mucosa or localized mucopurulent secretions were found. There was only one positive biopsy. Bronchial washings were reported in 9 cases and there was a cytologic diagnosis of malignancy in 2.

There were 20 operative cases. Three were reported at autopsy. Of the 20 operative cases, there were 9 lobectomy and 8 pneumonectomy. The other 3 patients were found to be nonresectable. The three nonresectable patients died three days, three months, and nine months, postoperatively. X-ray therapy was given the latter 2. The results of the 17 cases of resection are shown in Table II. Only 1 patient is known to have died of lymphosarcoma. Two others may have died of lymphosarcoma. Three have died of unrelated causes and 2 of these lived for thirteen years and nine months, and for four years, and seven months, respectively, without evidence of recurrence. Eleven patients are living an average of five and three-fourths years. There is no evidence of recurrence in 6 of these.

PATHOLOGY

Grossly, the tumor is a firm fleshy mass of white, pale yellow or gray-pink color. There is no capsule, and the tumor either merges into the surrounding pulmonary parenchyma or there may be fairly definite demarcation from the parenchyma.

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TABLE I. CLINICAL DATA ON 23 CASES OF PRIMARY LYMPHOSARCOMA OF THE LUNG

AUTHOR	AGE	SEX	X-RAY	SYMPTOMS	METASTASES	BRONCHOSCOPY AND CYTOLOGY
Anlyan, Lovingood, & Klassen	63	M	4 × 4 cm. increased density right lower lobe, sharply outlined, homogeneous	None	None	Negative Bronchial washings negative
Beck and Reganis	47	F	Discrete, smoothly rounded opacity in right lower lobe near costophrenic angle	None	None	No
Behrend*	59	F	Left lower lobe	Yes	None	Negative
Betts and Overholt*	—	M	Right upper lobe, massive	—	Yes	—
Blades*	—	M	Massive	—	Yes	Positive biopsy
Churchill	45	F	Right upper lobe, homogeneous, density extends from hilum to periphery	None	None	negative
Grimes	68	F	Left lower lobe, hazy density, indefinite borders	Cough 8 months, hemoptysis 3 months, DOE,† weight loss	None	Negative
Grimes	45	F	Left hilar well-defined mass with linear streaking peripherally	Mild chest pain after discovery of mass	None	Negative Cytology negative
Maier*	50	M	Left upper lobe, uniformly dense	None	None	Negative cytology
Ochsner and DeCamp*	66	M	—	—	Yes	—
Ochsner and DeCamp*	—	M	Left upper lobe	—	None	—
Ochsner and DeCamp*	50	F	Left upper lobe	—	None	—
Ochsner and DeCamp*	46	M	Right upper lobe	—	None	—
Pekelis	—	—	Left upper lobe, orange	None	Sternum, ribs, liver	None
Rose	75	F	—	Chest pain, easy fatigability, malaise	None	Cytology negative, malignant cells
Rose	38	F	—	None	None	Granularity and edema, negative biopsy, bronchial washings and 3 sputum tests negative

All of the above patients were proved to have lymphosarcoma of the lung on pathologic examination of resected lung or at autopsy.

*Cited by other authors.

†Dyspnea of effort.

(*Continued on next page.*)

TABLE I—CONT'D

AUTHOR	AGE	SEX	X-RAY	SYMPTOMS	METASTASES	BRONCHOSCOPY AND CYTOLOGY
Sarokhan	70	M	Lingula	Chronic cough	None	Negative bronchial washings
Spatt and Grayzel	34	F	Right lower lobe, infiltrative mottled, egg-shaped area of density	Hemoptysis 3 months, cough	None	Suppuration, no cytology
Sugarbaker			No details—Primary in lung			
Touroff	—	—	Right upper lobe, 5 cm.	—	None	—
Dvoracek	44	M	Right upper lobe, massive	None	Parietal pleura, pericardium, peribronchial and hilar nodes	Compression, bronchial washings positive
Weissman and Christie	52	M	Borders poorly defined, left upper lobe, massive	Cough 1 year, DOE† 6 months, weight loss 6 lbs.	None	Negative, bronchial washings negative
Willis	57	M	Large opacity, right upper lobe	Recurrent pneumonia, 3 years	Hilar and peribronchial nodes	—

All of the above patients were proved to have lymphosarcoma of the lung on pathologic examination of resected lung or at autopsy.

*Cited by other authors.

†Dyspnea of effort.

Microscopically, the tumor is composed of lymphocytes or lymphoblasts which replace the normal parenchyma. In the individual tumor the cells are of fairly uniform maturity. At the edges of the tumor the parenchyma is usually replaced in decreasing extent as it merges into the normal lung. As in 1 of our cases, there may be peripheral thin zones of fibrous tissue infiltrated by histiocytes. The neoplastic cells surround the vessels and bronchi but usually do not invade their walls.

No evidence of metastasis was found in 14 of the 23 cases. There was metastasis in all of the 5 autopsy and nonresectable cases. In 1 of the cases of resection, there was microscopic involvement of the peribronchial and hilar nodes. Recurrence in 4 of the patients who had resection has been mentioned.

CASE REPORTS

CASE 1.—G. W., a 38-year-old white housewife, was admitted to the Barnes Hospital May 5, 1955, for investigation of an enlarging density found in chest films and an aching in the right shoulder and arm for four months. She had had chest films yearly for the past five years. One year prior to her admission, x-ray had shown a density in the right upper lobe. She had a work-up for tuberculosis which was said to show old arrested tuberculosis. One month previous to admission, a repeat film showed enlargement of the mass. She was bronchoscoped, had bronchograms made, and was told that she needed an operation. She denied hemoptysis, cough, sputum, and shortness of breath. Review of systems and

TABLE II. RESULTS OF RESECTION IN CASES OF PRIMARY LYMPHOSARCOMA OF THE LUNG

AUTHOR	OPERATION	RESULT
Anlyan, Lovingood, and Klassen*	Right lower lobectomy	Four years after operation developed an area of increased density in right hilum which enlarged and was treated with x-ray with complete resolution 6 years after operation. No other evidence of recurrence.
Beck and Reganis*	Right lower lobectomy	A gastric ulcer present at the time of lobectomy showed complete healing. Two years after lobectomy the ulcer recurred. Subtotal gastric resection was performed and a section of the stomach was almost replaced by lymphosarcoma. The patient is living and well with no further evidence of recurrence 5½ years after lobectomy.
Churchill*	Right upper lobectomy	X-ray therapy postoperative. Five years later areas of opacity in both lungs treated with x-ray with marked regression. At 8½ years there is a homogeneous density in left costophrenic angles, right hilum has become larger for 2 years. At 8½ years both submaxillary glands are enlarged and are regarded clinically as lymphosarcoma.
Ochsner and DeCamp*	Left upper lobectomy	Died 4 years after operation. No other information available.
Rose	Right upper lobectomy	No evidence of recurrence 6 months after operation.
Sarokhan	Left upper lobectomy	Died 5 weeks after operation due to cerebrovascular accident.
Spatt and Grayzel*	Right lower lobectomy	Living without evidence of recurrence 14 months after operation, then lost to follow-up.
Touroff*	Right upper lobectomy	Well without evidence of recurrence 30 months after operation, then lost to follow-up.
Willis*	Right upper lobectomy	Developed empyema and was drained. Had x-ray therapy. Three years after operation had dime-sized area of granulation in right bronchus which cleared. Had more x-ray therapy. At present, 12 years after operation he has right main-stem bronchostenosis and some narrowing and deviation of left main-stem bronchus with purulent sputum on both sides.
Behrend*	Pneumonectomy	Well without evidence of recurrence 13 months after operation. Has since died but time and cause of death unavailable.
Grimes*	Pneumonectomy	Well with no evidence of recurrence 4 years and 3 months after operation.
Grimes	Pneumonectomy	Well with no evidence of recurrence 7 years after operation.
Maier*	Pneumonectomy	Well without evidence of recurrence 10½ years after operation. A nodule appeared in the right lung a few years after operation and disappeared with x-ray therapy. Again 3 years ago he developed a right paramediastinal density which disappeared with x-ray therapy. Survived 13 years and 9 months, died of coronary thrombosis.
Ochsner and DeCamp*	Pneumonectomy	There was never any clinical evidence of recurrence.
Ochsner and DeCamp	Pneumonectomy	Well with no evidence of recurrence 5 years and 8 months after operation.
Rose	Pneumonectomy	Died 4 years and 7 months after operation. Autopsy revealed no recurrence.
Weissman and Christie	Pneumonectomy	Died 2 years after operation of generalized lymphosarcoma.

*The follow-up information on these patients was obtained from the personal communications listed in the bibliography.

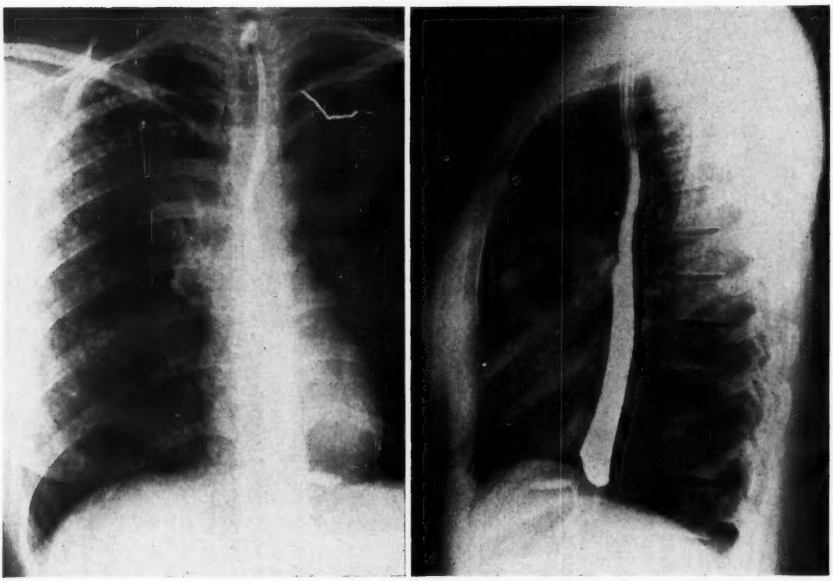

Fig. 1*A*.—Case 1. Admission films showing rounded density in the anterior segment of the right upper lobe.

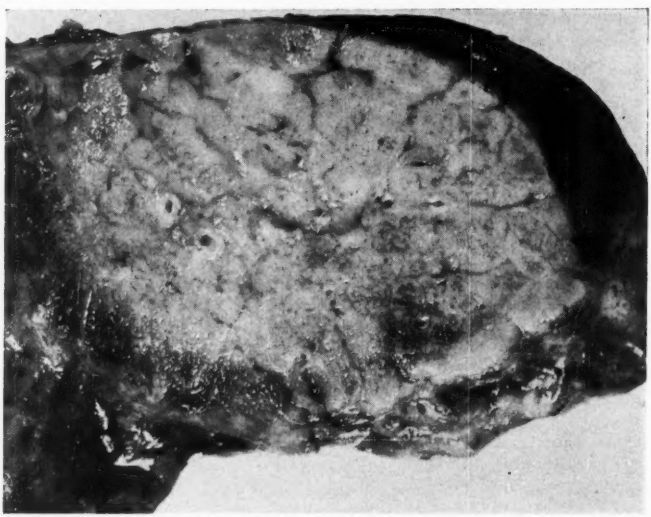

Fig. 1*B*.—Case 1. Firm tumor mass occupying anterior segment of right upper lobe.

past medical history was normal except for occasional intermittent attacks of epigastric and right upper quadrant cramping pain accompanied by nausea and vomiting and aggravated by fatty foods. There had been no weight loss.

Physical examination was normal except for an area of consolidation over the anterior right upper lung field (Fig. 1*A*). Laboratory data including hemoglobin, white blood cell count, peripheral blood smear, urinalysis, serum Kahn test, and electrocardiogram were normal. Bronchoscopy revealed a slight granularity and edema at the right upper lobe orifice. Biopsy of the right upper lobe spur, bronchial washings, and three sputum examinations were negative for acid-fast bacilli and tumor cells. Chest x-rays revealed a large, rounded mass in the right upper lobe adjacent to the mediastinum, interpreted as questionable right upper lobe atelectasis, questionable mediastinal thymoma.

On June 23, 1955, the patient was operated upon. The anterior segment of the right upper lobe was a solid mass. Frozen section showed lymphosarcoma. There were no palpable lymph nodes in the mediastinum or peribronchially. The right upper lobe was removed in routine manner. Postoperatively the patient made an uneventful recovery and was discharged on the thirteenth postoperative day.

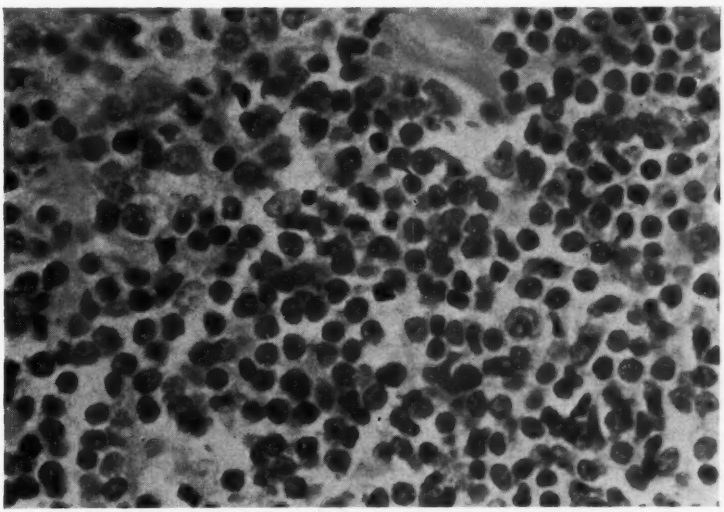

Fig. 1*C*.—Case 1. Photomicrograph showing almost complete replacement of the normal parenchyma by sheets and lobulated or nodular aggregates of small relatively mature and fairly uniform lymphocytes.

Grossly, there was a moderately firm tumor mass occupying the anterior segment of the right upper lobe extending into the adjacent apical and posterior segments (Fig. 1*B*). The margins of the tumor were distinct and accentuated by a 2 to 4 mm. zone of firm gray-yellow tissue. The cut surface of the tumor had a gray-pink color with mottling of gray-yellow, Microscopically, the excised rib showed normal marrow. Sections of the tumor showed almost complete replacement of the normal parenchyma by sheets and lobulated or nodular aggregates of small, relatively mature and fairly uniform lymphocytes (Fig. 1*C*). Mitoses were seen occasionally. Throughout the tumor were foci of patent alveoli with thickened walls invaded by lymphocytes. At the periphery of the tumor was a zone of dense fibrous tissue infiltrated by histiocytes. The neoplastic cells completely surrounded but did not invade the walls of the arteries, veins, bronchial glands, nerves, and bronchi. Seven hilar lymph nodes contained no tumor.

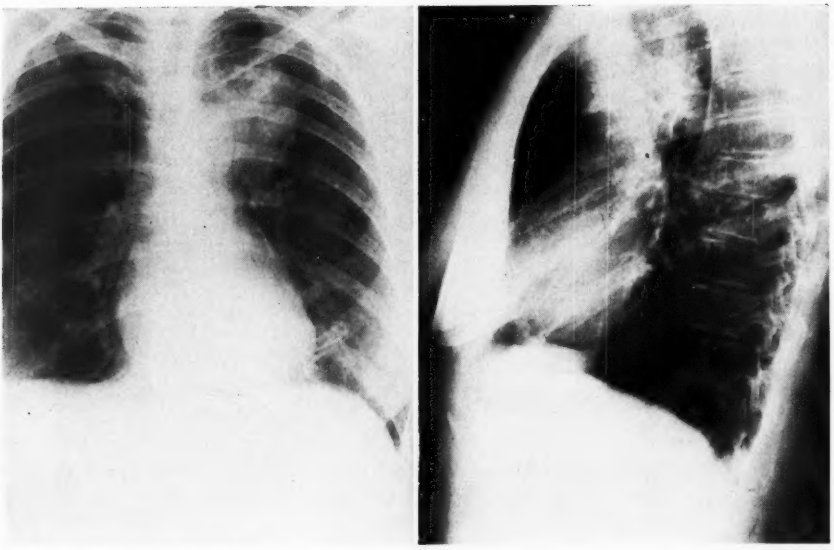

Fig. 2*A*.—Case 2. Admission films showing wedge-shaped area of increased density in the left upper lobe.

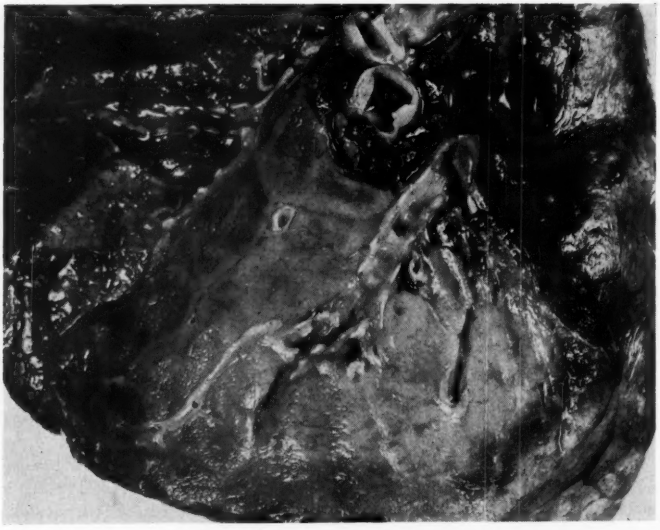

Fig. 2*B*.—Case 2. Wedge-shaped area of atelectasis containing the rounded fleshy tumor.

The patient has been seen in follow-up, and there is no evidence of recurrence by symptoms or fluoroscopy six months after operation.

CASE 2.—N. L. P., a 75-year-old married white woman, was admitted to the Barnes Hospital on Dec. 19, 1948. In June, 1948, she had onset of left chest pain associated with an upper respiratory infection. Easy fatigability and malaise were the only other symptoms. In October she consulted her physician because of recurrent left anterior chest pain, not associated with effort. Fluoroscopy showed a shadow in the left upper lung field. Review of systems and past medical history was noncontributory except that eleven years previously she had had a thyroidectomy for mild symptoms of toxicity with resultant good regression of her symptoms. Physical examination revealed a well-nourished, mentally alert elderly white woman. Chest was clear to percussion and auscultation. There was no clubbing of the fingers. The remainder of the physical examination was essentially negative. Routine laboratory data including a red blood cell and white blood cell count, hemoglobin, urinalysis, and peripheral blood smear were normal. Chest x-ray showed a wedge-shaped area of increased density in the left upper lobe (Fig. 2*A*). Bronchoscopy was performed on Dec. 21, 1948, with negative findings. Bronchial washings were taken and showed malignant cells.

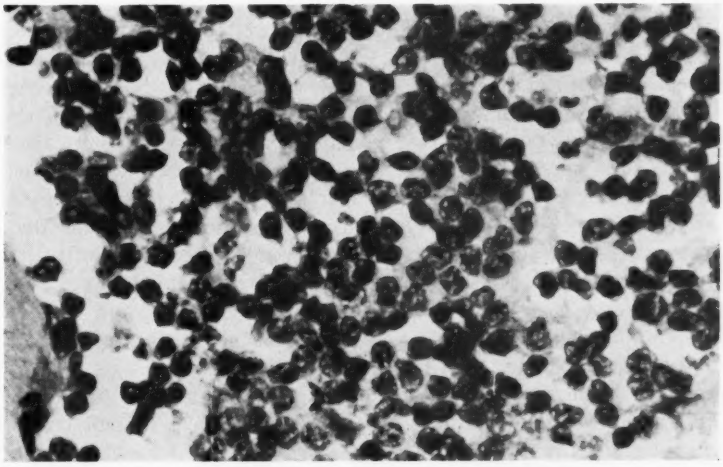

Fig. 2*C*.—Case 2. Photomicrograph showing replacement of the normal lung parenchyma by lymphocytes. Mitotic figures are frequent and there are a number of reticulum cells with prominent and multiple nucleoli.

Three sputum examinations for acid-fast bacillus and for tumor cells were negative. Venous pressure and circulation time were normal. Gastric fill-up was normal. Preoperative diagnosis was bronchogenic carcinoma. On Dec. 27, 1948, a left thoracotomy was performed. The superior anteromedial portion of the left upper lobe revealed a reddish-gray lung tissue under which a very firm mass could be palpated. The hilus was free. Pneumonectomy was performed. The patient's postoperative course was entirely uneventful.

Grossly, the specimen consisted of the entire left lung which weighed 395 Gm. In the upper lobe there was an atelectatic wedge-shaped area occupying the major portion of the apical segment of the upper lobe. There was a 6 cm. diameter, rounded, firm lesion palpable within the atelectatic segment. On cut section in the area of consolidation, there was a fleshy firm lesion approximately 6 to 7 cm. in greatest diameter (Fig. 2*B*). Grossly, the lung pattern appeared to be preserved and the lesion appeared to consist of a fleshy infiltration of the lung substance. There was no suggestion that the process arose within the bronchi. The lesion was fairly well demarcated from the surrounding lung tissue and was of pale yellow color, but around the periphery there were many punctate areas of yellow

color shading off into the normal lung substance. Microscopically, the tumor had erased the normal pattern of the lung and had invaded the alveolar walls in other areas. Mitotic figures were seen rather frequently and there were a number of reticulum cells which had prominent and multiple nucleoli and were rarely multinucleated (Fig. 2C). No eosinophils or fibrosis was seen. Immediately adjacent to the main tumor in otherwise fairly normal lung tissue there were many areas of focal infiltration of the same type of cells seen in the main tumor mass. These were located in the subpleural, perivascular, and peribronchial regions. Parenchyma of the lung was otherwise normal. In one area, blood vessel invasion was seen and in one large bronchus the tumor was growing beneath the intact epithelium around the cartilage and out into the lung substance. Five lymph nodes from about the upper lung bronchus showed reticulum-cell hyperplasia and no tumor cells. Other nodes from the lower lobe bronchus and from the hilum were negative.

In June, 1953, four years and seven months after operation, the patient was admitted to another hospital in a moribund condition. She died shortly thereafter. Autopsy revealed intestinal obstruction due to adhesions and the examination showed no evidence of lymphosarcoma.

DISCUSSION

Primary lymphosarcoma of the lung is distinctly different from the usual disseminated form of lymphosarcoma. It bears a similarity to lymphosarcoma of the stomach which often remains localized for long periods of time and may be cured by resection. Clinically, the lesion appears as an area of homogeneous increased density in the chest x-ray, which is not diagnostic. There are symptoms in less than one half of the reported cases. In only these instances has a diagnosis of malignancy been made preoperatively, one by bronchoscopic biopsy and two by cytologic sputum examination. At the time of operation the lesion may be recognized grossly as a neoplasm. Frozen section will identify its type.

There appears to be little difference in the recurrence rate between lobectomy and pneumonectomy. If the tumor is peripherally located and there are no grossly involved lymph nodes, lobectomy is recommended. Prognosis in resected cases is considerably better than for bronchogenic carcinoma.

Primary lymphosarcoma of the lung is another example of the need for exploratory thoracotomy in all cases in which there is a persistent unexplained lesion in the chest x-ray.

SUMMARY

Two patients with primary lymphosarcoma of the lung have been presented, with a summary of the literature. The need for exploratory thoracotomy in all cases in which there is an unexplained persistent lesion in the chest x-ray has been emphasized. The relatively good prognosis is apparent from this study.

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HISTOPATHOLOGIC OBSERVATIONS ON BRONCHIAL EPITHELIUM WITH SPECIAL REFERENCE TO CARCINOMA OF THE LUNG

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THE possibility that smoking is a cause of carcinoma of the lung is being intensively and widely discussed at present. In consideration of this question, the histologic changes produced in the lung by smoking are of fundamental interest, and for this reason we are presenting the results of a study that we have made of such changes in man.

When we first started this study, we planned to compare histologic sections from the lungs of smokers with sections from the lungs of nonsmokers, in a manner analogous to the procedure we have used to study the laryngeal epithelium of smokers and nonsmokers.[1, 2] Superficially, this approach of studying histologic sections from the lungs might seem to be an easy one, but in actual practice there are at least three major difficulties: First, there seem to be no answers to such questions as: What is the normal appearance of the bronchial epithelium? How thick should it be? What effect has age on the epithelium? Is there a difference between the bronchial epithelium of males and that of females? Is there a difference between the right and left sides? Is squamous metaplasia normal? How often does it occur in normal people? Is it more frequent with advancing age? These are but a few of the basic questions that have to be answered before a specimen of epithelium may be designated as abnormal or normal. The second major difficulty is that other conditions, such as chronic bronchitis, inhalation of industrial fumes, pulmonary edema, and terminal coma, affect the appearance of the bronchial epithelium. The third major difficulty is that of obtaining histories of smoking or nonsmoking that are reliable. Moreover, even after obtaining reliable histories, one has to be very careful to ascertain that the smokers are representative of *all* smokers and that some factor of selection has not entered into the study, as pointed out by Berkson.[3]

MATERIAL AND PROCEDURE

Because of the difficulties mentioned, we found it advisable to approach this problem mainly from a pathologic standpoint. We used four categories of specimens, and hence our observations are grouped as follows: (1) those

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made on the bronchial epithelium in routine (nontumor) necropsy specimens to obtain a base line and to set up criteria of normal; (2) those made on sections taken from the proximal portion of the bronchi in surgical specimens removed for conditions other than carcinoma; (3) those on the "normal-appearing" proximal portion of the bronchus in surgical specimens removed at pneumonectomy for one of three types of carcinoma, namely, squamous-cell carcinoma, adenocarcinoma, or small cell carcinoma; and (4) those made on necropsy specimens obtained from the good lung in cases in which carcinoma of the other lung had been treated surgically.

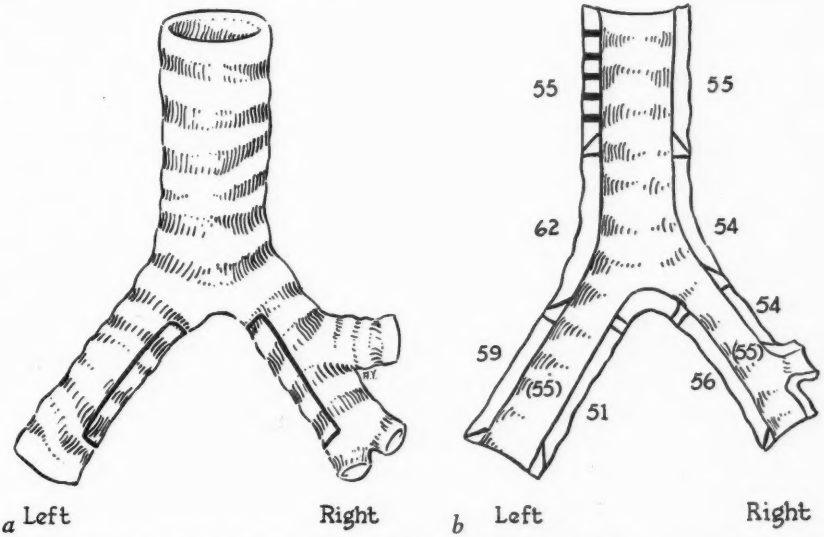

Fig. 1.—*a*, Drawing to show where sections were taken from the posteromedial wall of the main-stem bronchi of the routine necropsy specimens. *b*, Drawing to show where sections were taken from the lateral and medial walls of the trachea and primary bronchi of non-smokers. The numbers represent the average thickness, in microns, of the epithelium in the corresponding segments, with the numbers in parentheses representing the over-all average figures for the respective main-stem bronchi.

As demonstrated by Proetz,[4] and later by Ermala and Holsti,[5] smoke behaves according to certain predictable patterns. The tars settle out at sites where eddy currents are set up by changes in direction of flow of the smoke or in cross-sectional areas of the conducting system. We felt that one such site, and one that is readily accessible for examination, is the medial and slightly posterior portion of the main-stem bronchi; consequently, we chose this site for study. From the necropsy specimens, a longitudinal strip approximately 3 to 5 cm. in length was removed from the posteromedial wall of each bronchus (Fig. 1, *a*). Longitudinal sections of these strips were made and stained with hematoxylin and eosin. The slides were identified only by number, so that the observers had no knowledge about the individual represented by a particular slide. Of necessity, the strips of tissue removed from the surgical specimens were shorter than those obtained from the necropsy specimens, as

TABLE I. THICKNESS OF EPITHELIUM IN 387 BRONCHI (294 SUBJECTS)

	NECROPSY SPECIMENS WITHOUT CARCINOMA OF LUNG				SURGICAL SPECIMENS						NECROPSY SPECIMENS WITH CARCINOMA OF LUNG					
	NORMAL*		ROUTINE		SQUAMOUS-CELL CARCINOMA		ADENO-CARCINOMA (AND ADENOMA)		SMALL-CELL CARCINOMA		OPPOSITE LUNG		LUNG WITH TUMOR (BRONCHIAL STUMP)		TOTAL	
	NO.	MEAN†	NO.	MEAN†	NO.	MEAN†	NO.	MEAN†	NO.	MEAN†	NO.	MEAN†	NO.	MEAN†	NO.	MEAN†
Males																
Left	5	55	65	64.6	25	72.6	13	66.8	21	70.3	21	79.4	5	77.0	155	67.3
Right	5	55	61	70.2	23	64.0	25	69.1	16	71.5	15	73.1	11	80.9	156	68.2
Females																
Left			28	60.8			9	67.6	1	75	3	66.7	1	60	42	63.4
Right			29	60.5			2	70			2	52.5	1	65	34	60.7
Total	10	55	183	65.2	48	68.4	49	68.2	38	70.9	41	74.9	18	77.8	387	66.7

*Normal as defined in the text.
†Mean epithelial thickness in microns.

we were careful, in removing the strips beginning at the proximal end of the bronchi in the surgical specimens and extending distally toward the tumor, to stop well short of the visible margins of the tumor; the reason for this care is the fact that, as pointed out by Habein,[6] a zone of carcinoma in situ often extends out from the tumor but remains in continuity with the primary lesion. By the use of a stencil, ink marks were placed on each slide to designate the areas where the epithelial thickness was to be measured. Measurements were made only in those areas where no erosions or artifacts were present; for example, we have observations on the incidence of squamous metaplasia occurring in the bronchus of 30 left lungs removed because of squamous-cell carcinoma, but determinations of epithelial thickness were made on only 25 of these lungs.

In the previous studies of the effect of smoking on the larynx[1, 3] there were 5 persons who, it seemed certain, were nonsmokers and from whom bronchial tissue was preserved. In 2 of these cases a strip of tissue was removed from each main-stem bronchus, as was done in the routine necropsy cases mentioned above, but in the other 3 cases, additional strips were removed from the lateral walls of the distal part of the trachea and the proximal portions of each bronchus (Fig. 1, *b*).

RESULTS

Routine Necropsy Specimens.—In the routine (nontumor) necropsy specimens, squamous metaplasia was not frequently encountered. It was present in 6 of the 77 males (7.8 per cent), or in 4 of 65 left bronchi and in 5 of 61 right bronchi. It was found in 2 of the 36 females (5.6 per cent), or in one of 28 left bronchi and in 2 of 29 right bronchi. No evidence of malignancy was seen in any of the routine necropsy specimens, either from males or from females. The data on thickness of the bronchial epithelium are given in Table I.* It is to be noted that the bronchial epithelium from the routine necropsy specimens was thicker in the males than in the females, and that while the bronchial epithelium on the right was of the same thickness as that on the left in the females it was thicker than that on the left in the males. These subjects were distributed through the second to tenth decades of life inclusive, with the majority being rather evenly distributed through the fifth to ninth decades. We found no consistent relationship between age and epithelial thickness, or between age and the occurrence of squamous metaplasia in these routine necropsy specimens.

In Table I, under the heading "Necropsy specimens without carcinoma of lung" and under the subheading "Normal," 10 specimens (5 cases) are listed. All 5 patients were males. Two of the 5 were farmers, one was a barber, one was a carpenter and one had been an inmate of a state mental hospital for many years. The carpenter lived in a town of less than 25,000 population and the others were essentially rural residents, living in towns of 2,000 or 3,000 population. Thus, urban living, in its usual sense, was ruled

*Detailed tables on epithelial thickness of specimens in all four categories, arranged according to distribution of patients by age, will be supplied by the authors on request.

out in all 5 individuals. None of the 5 subjects gave a history of inhaling industrial fumes, and all were nonsmokers. The average thickness of the bronchial epithelium of these 5 individuals was 55 μ for both the right and the left main bronchus. Fig. 2 is from one of these subjects and shows what we believe to be normal-appearing bronchial epithelium for males 40 to 65 years of age.

Surgical Specimens From Cases of Noncarcinomatous Disease.—In 50 cases in which a section was taken from a lung that had been removed surgically because of some condition other than carcinoma, the most striking finding was the presence of squamous metaplasia in more than 80 per cent of cases. This metaplasia was of a very mature, well-differentiated type and was not at all suggestive of malignancy. Most of these lungs had been removed because of such diseases as bronchiectasis, tuberculosis, and abscess of the lung, and with the overwhelming amounts of infection present the bronchial epithelium was too eroded to permit of reliable measurements of epithelial thickness; hence, this category of observations is not represented in the Table.

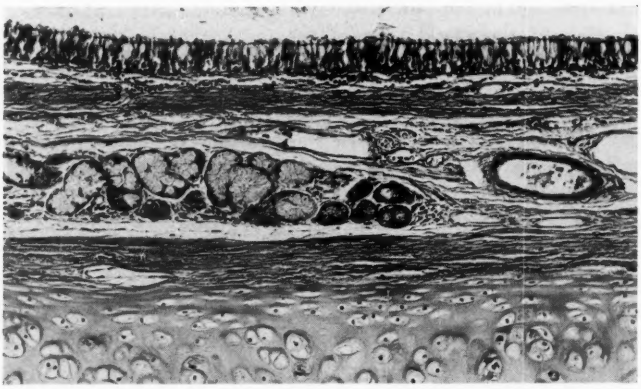

Fig. 2.—Normal bronchial epithelium from a 63-year-old white man. The subject was a farmer (lived in a rural area) and was a nonsmoker (hematoxylin and eosin; ×100).

Surgical Specimens From Cases of Carcinoma of the Lung.—Squamous metaplasia was present in the sections taken proximal to the site of squamous-cell carcinoma in 43 of 55 surgical specimens (78 per cent). These specimens were all from males, and the squamous metaplasia was present in 22 of 30 left main-stem bronchi and in 21 of 25 right main-stem bronchi. An in situ carcinoma, separate and discrete from the primary, was present in one right bronchus and in one left bronchus. Much of the metaplasia was atypical, with marked hyperplasia and loss of polarity of cells; the metaplasia was not of the mature, well-differentiated type seen in the bronchi associated with inflammatory lesions. As shown in Table I, the epithelial thickness averaged 68.4 μ in the 48 specimens in which it could be measured.

Squamous metaplasia was present in 34 per cent of the 49 specimens in which there was adenocarcinoma (or adenoma). It was present in only one

of the females, that being on the left side, but it was present in 12 of 25 right-sided specimens and in only 4 of 13 left-sided specimens from males. Fig. 3 represents a section from the left lung of a 41-year-old man who had an adenocarcinoma of the cylindroma type; this is the only carcinoma in situ found in the sections removed proximal to an adenocarcinoma. The picture shows squamous metaplasia of the surface epithelium, with a squamous-cell variety of an in situ lesion in the ducts.

Of 38 lungs removed because of small-cell carcinoma, squamous-cell metaplasia was present in 27, or 71 per cent. In the single specimen from a female there was no squamous metaplasia, but in 17 of 21 left lungs and in 10 of 16 right lungs from males there was metaplasia. No in situ lesions were found in these cases but, as in the cases of squamous-cell carcinoma, the metaplasia was not of a mature and well-differentiated type.

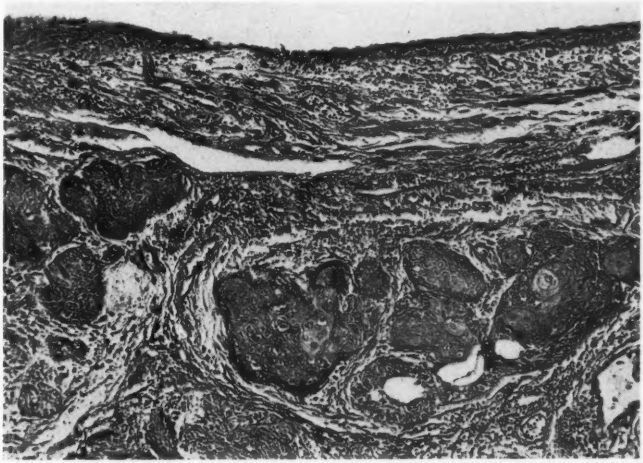

Fig. 3.—Squamous metaplasia of the bronchial epithelium, with an in situ carcinoma present in the ducts. This section is from the proximal portion of the bronchus of a lung removed because of a cylindroma type of adenocarcinoma in a 41-year-old man.

Necropsy Specimens From Opposite Lung in Carcinoma of Lung.—In 41 cases in which the subject had undergone surgical removal of a carcinoma of the lung we were able to obtain tissue from the untreated (opposite) lung at necropsy. In 18 of these cases a segment of bronchus had been left at the time of surgical removal of the primary tumor (Table I). Sixteen of the males and 2 of the females had squamous metaplasia in the "good" lung, which more often was the left lung. In 5 cases an in situ or a frank carcinoma was present in the strip of tissue taken from the "good" lung. These lesions were found only on microscopic examination, the bronchus appearing quite normal on gross examination. In these cases the epithelium was thicker than that encountered in any other group of cases. Also in these cases, basilar hyperplasia, marked hyperplasia, atypical metaplasia and in situ carcinoma in ducts were evident (Figs. 4 and 5). In fact, all degrees of progression from benign

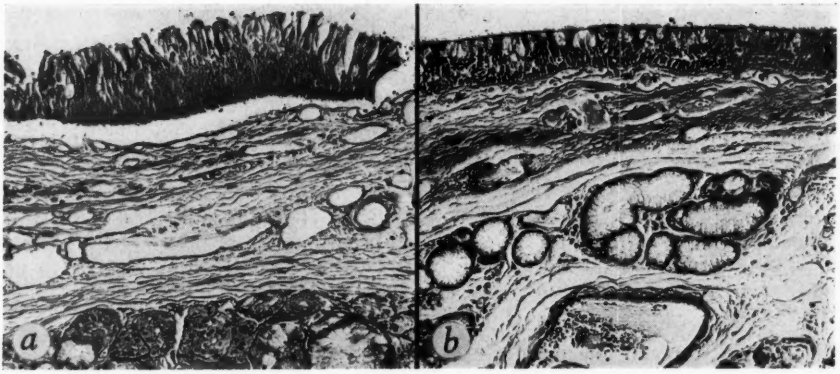

Fig. 4.—*a*, Marked basilar hyperplasia of the bronchial epithelium of the left main-stem bronchus. The patient had a squamous-cell carcinoma of the right lung (hematoxylin and eosin; ×100). *b*, Moderate basilar hyperplasia of the bronchial epithelium. This specimen is from the right lung of a 60-year-old man who had a squamous-cell carcinoma of the left lung (hematoxylin and eosin; ×100).

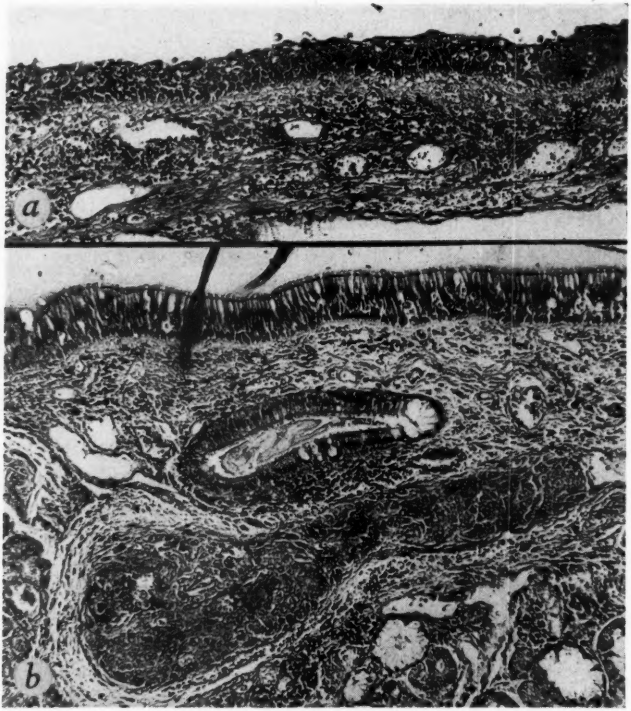

Fig. 5.—*a*, Hyperplasia and atypical metaplasia of the bronchial epithelium of the left lung from a 62-year-old man having a squamous-cell carcinoma of the right lung (hematoxylin and eosin; ×100). *b*, Hyperplasia of the surface epithelium and an in situ carcinoma in a bronchial gland. This specimen is from the right lung of a 65-year-old man who had a squamous-cell carcinoma of the left lung (hematoxylin and eosin; ×100).

basilar hyperplasia to frank carcinoma such as has been described in the uterine cervix can be seen in our sections from these opposite or "good" lungs. Fig. 6 portrays sections from a 63-year-old white man who underwent right pneumonectomy for a squamous-cell carcinoma in 1949. In 1952, the patient was found to be well and presented no evidence of any recurrence of his disease. While he was eating in a downtown restaurant, he aspirated a bolus of meat and died of asphyxia. At necropsy the left bronchus appeared normal on gross examination, but the photomicrographs show that pathologic changes were present; the patient did not live long enough for the lesions to become symptomatic.

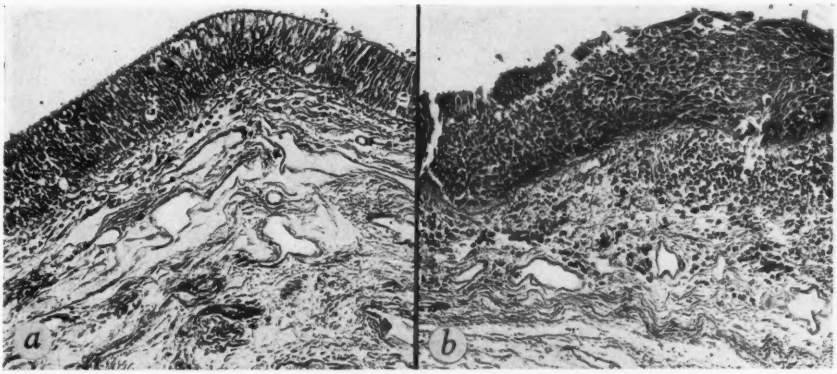

Fig. 6.—*a*, Marked hyperplasia of the surface epithelium of the left main-stem bronchus in a 63-year-old man who had undergone right pneumonectomy for squamous-cell carcinoma some three years previously (see text for details). In 1952, while he was in town for a checkup, he died of asphyxia from a bolus of meat. Post-mortem examination disclosed no gross evidence of residual carcinoma (hematoxylin and eosin; ×100). *b*, Photomicrograph of bronchial epithelium from the left lung of the same subject as in *a*. This area adjacent to the tissue shown in *a* shows marked squamous metaplasia with an in situ carcinoma of the surface epithelium.

COMMENT

At the time this study was undertaken, almost two years ago, we were not familiar with any similar attempts to evaluate the effects of tobacco on the lungs. Subsequently, we found three other studies of a somewhat similar nature. The first is the report of Wittekind and Strüder,[7] who studied surgical and necropsy specimens to see if smoking produced any effect on the bronchi. These authors concluded that no relationship existed between tobacco smoking and the bronchial structure. They felt that squamous metaplasia and any other pathologic changes present were due to chronic bronchitis. They did find a high percentage of smokers among those having carcinoma of the lung. In 4 of their cases there were small, in situ cancers in addition to the larger and obvious tumor of the lung. The second study is that of Weller,[8, 9] in which 21 sections were taken from the lungs in a set pattern at necropsy. The sections of epithelium were studied microscopically for squamous metaplasia, both typical and atypical, and the findings were then correlated with age, sex, occupation, smoking habits, and place of residence. With 21 sections, Weller found a much higher incidence of squamous metaplasia than we have observed

in our routine necropsy cases, in which only one block was removed from each main-stem bronchus. In neither of the two reports do the authors give any data on thickness of the bronchial epithelium in microns. The third report is that of Auerbach and associates,[10] who found that smokers had thicker bronchial epithelium and also a higher incidence of metaplasia than did nonsmokers.

In our study, we found that the bronchial epithelium is thicker in the male than in the female, which corresponds to the findings in our studies on the laryngeal epithelium. We found no consistent relationship between thickness of the bronchial epithelium and age.

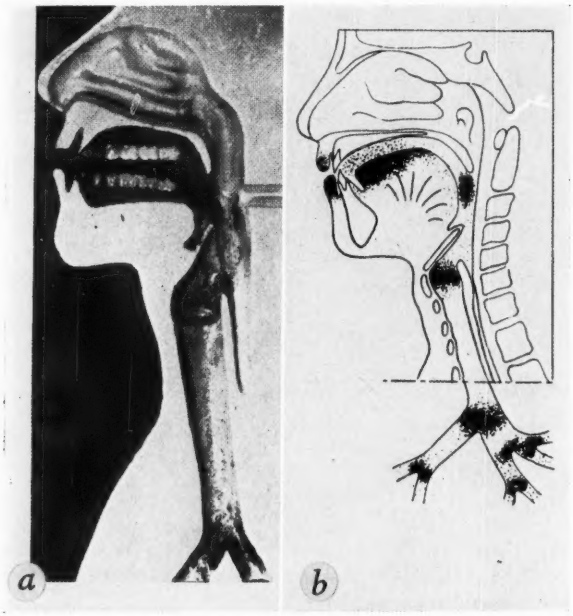

Fig. 7.—*a*, Plastic model of the respiratory tract showing the deposition of tobacco tars. *b*, Sketch showing the sites of carcinoma of the respiratory organs. (From Ermala, and Holsti: Cancer 8: 674-678, 1955.)

In the routine necropsy cases, the finding of squamous metaplasia in 7.8 per cent of the cases is in sharp contrast with the finding in the surgical specimens from cases of carcinoma of the lung, in which 78 per cent of the squamous-cell carcinomas (all males), 34 per cent of the adenocarcinomas, and 71 per cent of the small-cell carcinomas were associated with squamous metaplasia of the bronchial epithelium proximal to the tumors. Much of this might be explained on the basis of irritation and secondary infection due to the tumors, but this basis is inadequate to explain the 44 per cent incidence of squamous metaplasia or the 12 per cent incidence of in situ or frank carcinoma in what appeared grossly to be normal surface epithelium in the opposite (good) lung.

It is interesting that the epithelium of the right main-stem bronchus was thicker than that of the left in the males of the routine necropsy series. Although the increase in thickness in the cases of carcinoma was not as great as in the routine necropsy series, the average figures for the right side were more than those of the left. It is also to be noted that the over-all incidence of squamous metaplasia was greater on the right than on the left side, with more occurring in males than in females. It was our feeling that in most cases squamous metaplasia seemed to start at or near the opening of ducts and occasionally in the bronchial glands.

In our previously reported study of the larynx we noted that squamous metaplasia was present in the false cord or subglottic area in about one half of the male larynxes and in one fourth of the female larynxes. It is certainly an attractive speculation that some agent in the inspired air is one of the main causes of squamous metaplasia of the respiratory tract, with a high incidence of such lesions in the larynx, where concentration of the agent would be very high, and a much lower incidence in the main-stem bronchi, where considerable dilution has taken place. One would not expect such an agent to have much effect on most of the trachea, as this is a relatively straight tube in which no eddy currents or areas of turbulence should be present to cause the agents, such as tars in tobacco smoke, to be deposited on the walls. The work of Ermala and Holsti[5] is interesting in this light. They made a plastic model of the respiratory tract and, coating it with egg albumen, made it smoke; this caused the inspired tars to be deposited in the larynx and main-stem bronchi, as shown in Fig. 7, *a*. Fig. 7, *b* shows the areas where carcinoma occurs in the respiratory tract. These authors state that there is a "striking correlation noted between the clinical frequency of cancer and the localization of the tobacco smoke, especially in view of smoking habits."

Another observation of great interest in our study is the relatively high incidence of in situ lesions or small carcinomas in the opposite (good) lung in cases of carcinoma of the lung. Is carcinoma of the lung a multicentric disease? These patients did not live long enough for the lesions in the opposite lung to assume clinical significance. The question comes up; How long does it take pulmonary lesions to develop? Does it take years, as in the case of in situ lesions of the uterine cervix?

Finally, this study raises the question of how much of the bronchial epithelium proximal to a tumor should be removed. This is most important in the cases of squamous-cell carcinoma and small-cell carcinoma, in which a high incidence of atypical squamous metaplasia was seen in this study. Changes of this nature seem to be one more indication for pneumonectomy rather than lobectomy in these cases, if such is at all feasible.

SUMMARY AND CONCLUSIONS

This study shows that in the absence of irritants such as industrial fumes and smoking the normal bronchial epithelium of males is a pseudostratified columnar epithelium about 55 μ thick. In routine necropsy cases the thickness of the epithelium is about 67 μ in males and 60 μ in females. The epi-

thelium in the male is almost always thicker than that of the female, and in the males the epithelium of the right bronchus tends to be thicker than that of the left. The incidence of squamous metaplasia was approximately 8 per cent in the routine necropsy cases of this study. The epithelium proximal to a carcinoma and the epithelium in the opposite (good) lung tend to be thicker and more hyperplastic and to present a much higher incidence of squamous metaplasia, much of which is atypical, than does the normal bronchial epithelium. A 12 per cent incidence of in situ or frank carcinoma was found on microscopic examination of the opposite ("good") lung in cases of carcinoma of the lung even though the bronchi appeared normal on gross examination.

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RESISTANCE TO AIR FLOW IN BRONCHOSPIROMETRIC CATHETERS

E. W. Swenson, M.D., and G. Birath, M.D.

With the Technical Assistance of A. Åhbeck

GAENSLER and his associates[1] have studied certain physical principles bearing on breathing against the resistance due to the turbulent type of flow ordinarily encountered in bronchospirometric catheters, and have shown that any decrease in airway diameter results in a marked increase in resistance. The various catheters tested by these authors exhibited from four to eighteen times the resistance of the normal human airway. The Carlens tube[2] was found to be superior in this and other respects to the Norris,[3] Zavod,[4] and Gebauer[5] catheters.

The Marsh catheter[6] was introduced subsequent to the study just mentioned[1] and, in addition to certain mechanical improvements, was said to have less resistance to breathing than others; however, no data were given to support this statement. Since bronchospirometry has been utilized extensively in this laboratory, it was decided to investigate and compare the airflow resistance characteristics of the various catheters, including that of Marsh, using both moist and dry air; moist air is usually respired during bronchospirometry and the influence of its increased density was not investigated by Gaensler and his co-workers.

METHODS

The apparatus used was similar to that of Gaensler, and is shown in Fig. 1. The only major modification was an effort to saturate the air flowing from the tank with water vapor. Studies were also made for comparison using dry air.

The flow rate, controlled at the valve of a compressed air tank, was varied between zero and 50 L. per minute and measured with a calibrated flow meter.* The maximum figure was derived from the highest minute ventilation value observed in our series of over 500 bronchospirometries, and from multiplying this value by 3.3 to estimate maximum rate of flow occurring during the respiratory cycle.[7] Pressures existing in the system were measured at the various flow rates without catheter and with each lumen of the following catheters:

CATHETER	EXTERNAL DIAMETER (MM.)	INTERNAL CROSS-SECTIONAL AREA ($CM.^2$)	
		RIGHT	LEFT
Carlens 41 Fr.	15	0.44	0.45
Carlens 39 Fr.	13	0.38	0.36
Carlens 37 Fr.	12.5	0.31	0.33
Marsh	14	0.28	0.27
Zavod	12	0.20	0.20

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*Model G 9148B, Emil Greiner Co., New York 13, New York.

Pressures were recorded in each case as Δ P in centimeters H_2O, the difference between the observed pressure within the system with the catheter in place and the pressure found at the same flow rate when no catheter was present.

RESULTS

Fig. 2 graphically portrays the back pressures exerted due to resistance in each catheter lumen at the various flow rates for *dry* gas. In Fig. 3 the same data are presented with the pressures plotted on a square scale; the relationship between flow and pressure becomes almost rectilinear except for the Carlens 41 catheter (see discussion) and the first part of the curves during slow rates of flow. Each of the two lumina of the Marsh catheter have somewhat more resistance than do those of any of the Carlens tubes, and somewhat less than those of the Zavod catheter.

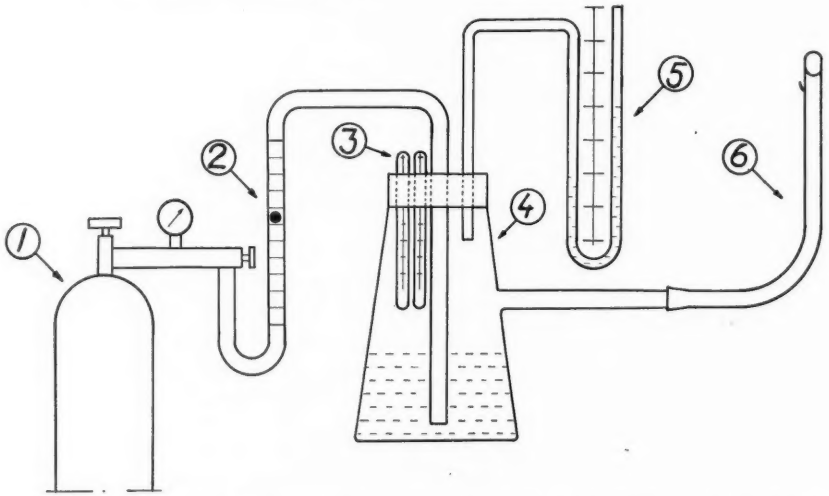

Fig. 1.—Arrangement of apparatus to measure pressures due to resistance to air flow in bronchospirometric catheters. Air flow was controlled at the compressed air tank (*1*) and measured at the flowmeter (*2*). Saturation of the air with water vapor took place when the air bubbled through water in a large flask (*4*) and was measured with a psychrometer (*3*). For each flow rate, back pressure, *P*, due to the catheter (*6*) was read at the manometer (*5*).

Similar relationships between the various catheters are noted when moist air is used instead of dry. During this second series of experiments, psychrometer readings ranged from 92 to 99 per cent relative humidity at the various flow rates. All pressures are relatively higher than those found when dry air is used (Fig. 4).

DISCUSSION

The back pressure, Δ P, resulting from a given nonturbulent, uniform flow through a smooth, straight tube is predictable in accordance with

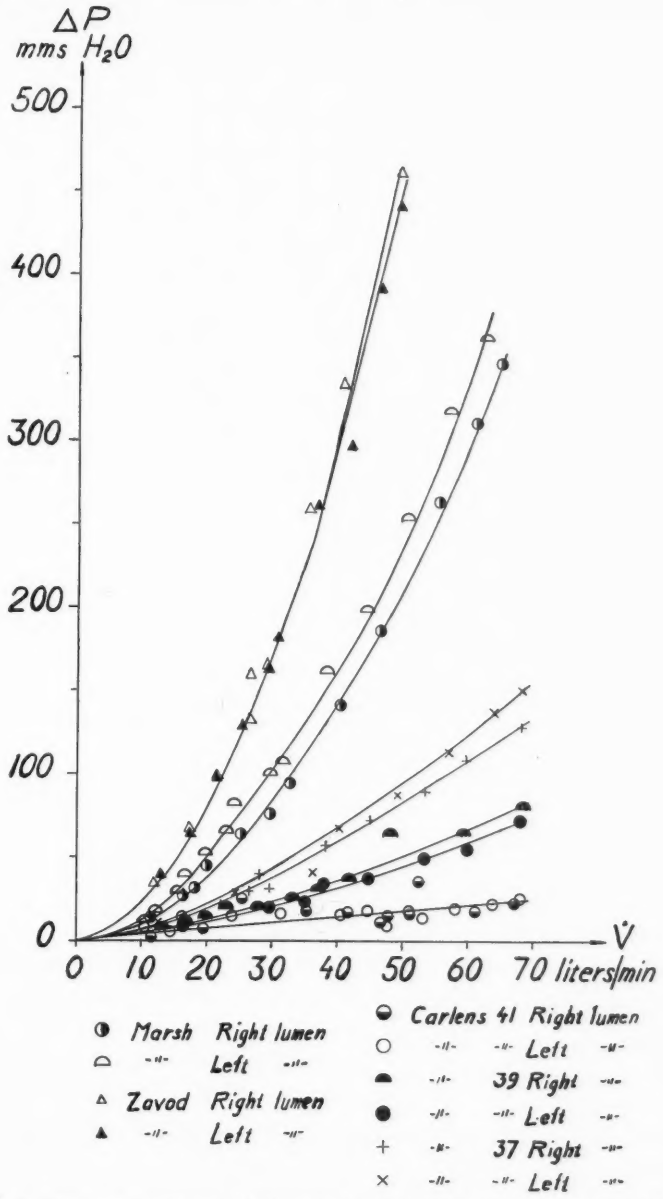

Fig. 2.—Flow rate-resistance relationships in various bronchospirometric catheters. Dry air. The tubes with smaller diameters develop high resistance ($\triangle P$) as the flow rate ($\dot{V}$) is increased. The curves of the high resistance tubes indicate turbulent flow whereas the larger catheters allow streamline flow.

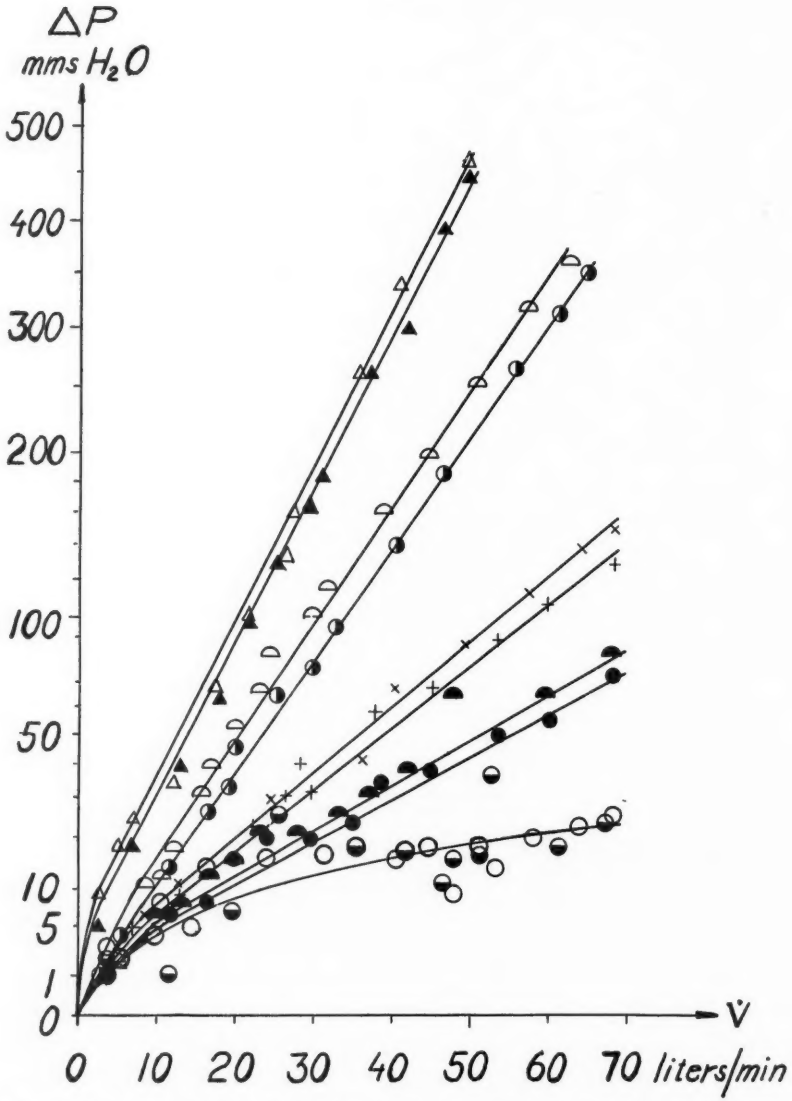

Fig. 3.—Flow rate-resistance relationships in various bronchospirometric catheters. Dry air. Data shown in Fig. 2 are plotted with back pressures on a square scale. (See text.)

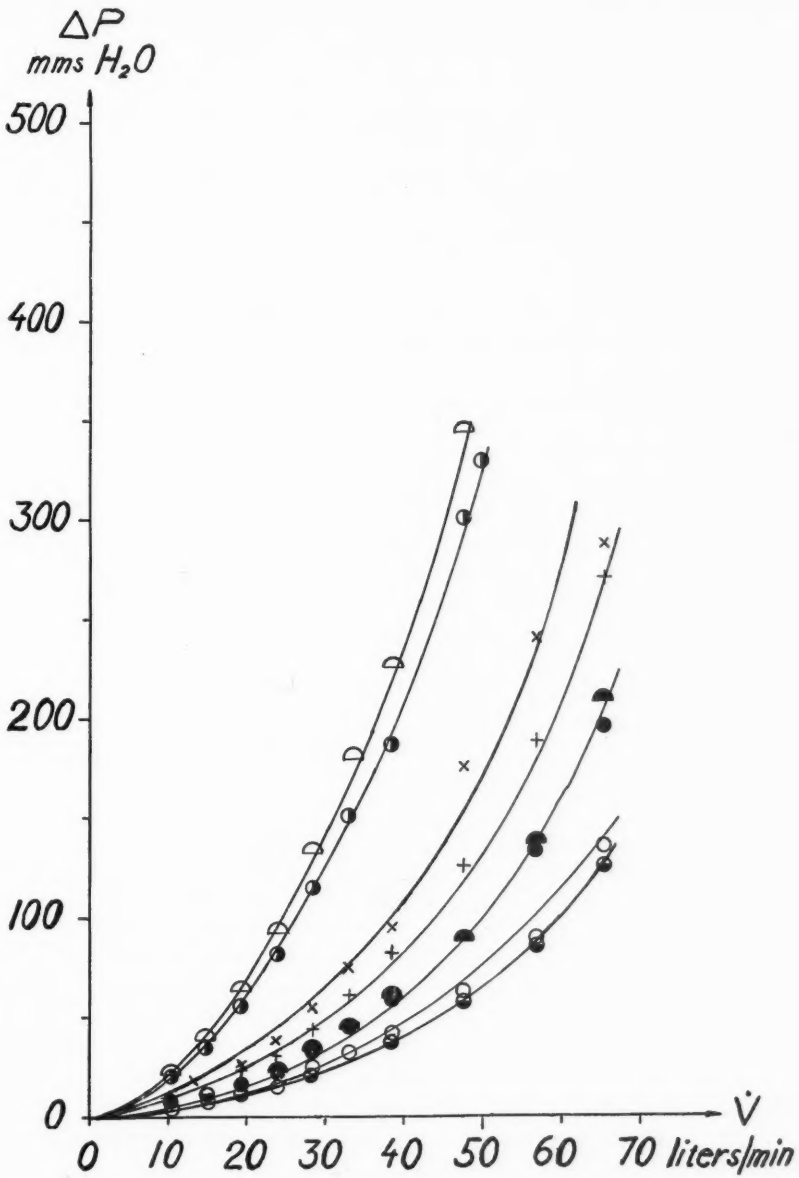

Fig. 4.—Flow rate-resistance relationships in the same bronchospirometeric catheters. Moist air. The resistance of each tube is again seen to be related to its internal cross-sectional dimensions. However, the addition of water vapor (simulating conditions of clinical use) results in turbulent flow at all flow rates and consequently a sharply increased resistance even in the large lumen catheters.

Poiseuille's law as long as the pressure exerted on the gas remains the same. The law states:

$$\Delta P = \frac{8 \dot{V} l \mu}{\pi r^4}.$$

Where $\dot{V}$ is the flow rate, l is the length of the tube, μ is the viscosity of the gas, and r is the tube's internal radius.

Of particular importance is the exponential relationship of the resultant back pressure to the radius of the tube; this means that any decrease in tube width (internal diameter) greatly increases the resistance to a given flow. Also noteworthy is the *linear* relationship between pressure and volume flow rate during laminar flow.

However, the departures from the conditions of this law which pertain in the human airway cannulated with a double lumen catheter are significant. (1) The airways leading from the patient to the spirometers are not straight but curve gently at the pharynx and in the tubing and adapters leading to the spirometers. At each opening of the catheter and at each adapter between the tube and the spirometer, orifice turbulence can also arise with resultant increase in total resistance. (2) The flow rate of the gas is not uniform but may range during each respiratory cycle from 50 L. per minute in one direction (inspiration) to 40 L. per minute in the opposite direction (expiration).

Except for the slowest flow rates in the largest tubes studied, the relationship between flow and back pressure is not rectilinear (see Fig. 2), indicating the existence of turbulent flow. The Fanning equation for back pressure resulting from turbulent flow states:

$$\Delta P = \frac{f \cdot v^2 \cdot l}{r} = \frac{f \cdot \dot{V}^2 \cdot l}{\pi^2 \cdot r^5}$$

Where v is the linear velocity $= \frac{\dot{V}}{\pi r^2}$, f is a friction factor, and ΔP, $\dot{V}$, l, and r are as defined previously.

Thus, the relationship between back pressure and turbulent flow rates is a square one; this effect of turbulence is shown in the curves of Fig. 3 at the higher flow rates (except for the Carlens 41 lumina). The internal dimensions of the tube are seen to assume an even higher exponential (fifth power) relationship to the back pressure developed than in nonturbulent flow.

It should also be stressed that moist air, because of its increased density in comparison with dry air used in previous studies, heightens the tendency toward turbulent flow and thus increases the resistance encountered. As seen in Fig. 4, the flow in the catheters is always turbulent at the flow rates encountered and when moist air is present in the closed respiratory system. The importance of using the largest possible catheter lumina is thus clearly seen.

CONCLUSIONS

1. Resistance to air flow was measured in the lumina of the Zavod, Marsh, and Carlens (3 sizes) bronchospirometric catheters. The range of flows in the experiments was that which had previously been found in clinical use of the

tubes. The findings of Gaensler[1] were confirmed, in that there exists a rectilinear relationship between the square of the flow rate of dry air through the tube and the resistance against it, indicating the presence of turbulent flow. However, the large size Carlens catheter allowed streamline flow at all flow rates of dry air.

2. Moist air, because of its increased density, heightens the tendency to turbulent flow, and thus the resistance to flow, as compared to dry air used in previous investigations. Turbulence is thus encountered under conditions of clinical use in even the largest catheters and at the slowest flow rates.

3. The Carlens catheters caused less resistance to air flow than the Marsh or Zavod tubes. This superiority, with its evident implications to clinical evaluation of comparative unilateral lung ventilation, is readily predictable from the larger cross-sectional dimensions of their lumina. Since, under conditions of turbulent flow, the resistance developed in any catheter lumen is proportional to the fifth power of its radius, small differences in tube design assume considerable importance.

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THE TRACHEAL BRONCHUS

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IN many mammals a bronchus arises directly from the right side of the trachea; in man this is an anomaly. Flint[1] made an extensive study of the embryology of the pig's lung and beautifully illustrated this tracheal bronchus, which he called Lateral 1 (Fig. 1). Hare[13] demonstrated a similar bronchus in a sheep's lung (Fig. 2). Bremer[2] found that about 5 per cent of human embryos over the 5 mm. size showed one or occasionally two tracheal outpocketings, usually on the right. He reasoned that they probably regressed since these bronchi are rare in the newborn infant.

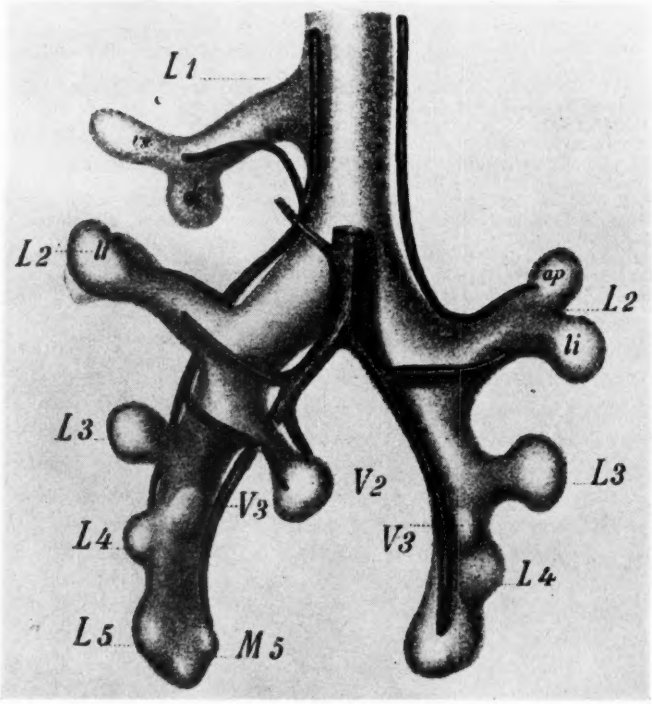

Fig. 1.—Reconstruction of the bronchial tree of a pig 13.5 mm. long. (From original of Fig. 15, J. M. Flint, Am. J. Anat. 6: 1-138, 1906.)

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Received for publication Feb. 15, 1956.

There has been some discussion about what to call this tracheal bronchus. Boyden[3] employs the term "pre-eparterial" for bronchi that arise from the trachea or from the right primary bronchus proximal to the right upper lobe bronchus. Foster-Carter[4] uses a nomenclature that requires an exact anatomic analysis of the segments of the lung involved. When one of the segments or subsegments of the right upper lobe, usually the apical segment, is displaced onto the trachea, he refers to it as a "displaced bronchus"; if the right upper lobe has all its normal segments, the tracheal bronchus is called a "supernumerary bronchus."

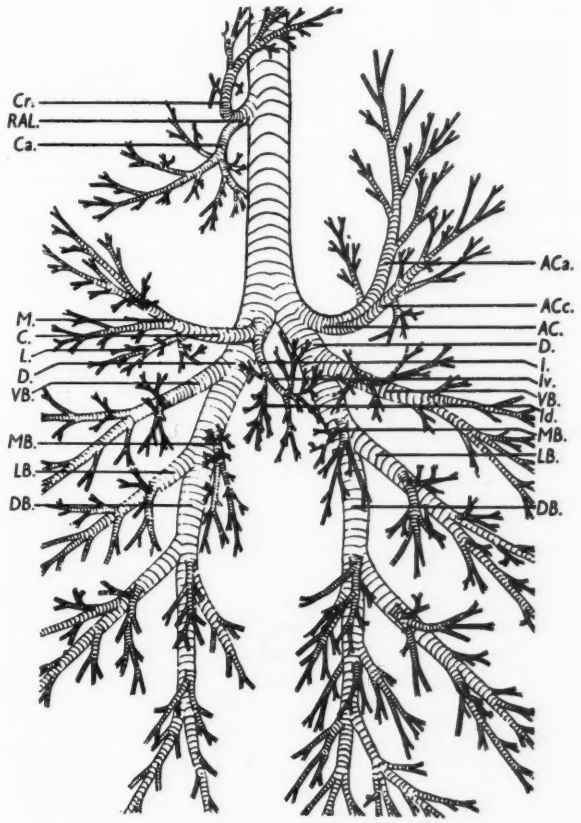

Fig. 2.—After Hare. Ventral view of the bronchial tree in the sheep showing the right apical lobar bronchus (RAL). (Published by permission of the J. Anat.)

The "displaced bronchus" is a common anomaly; the supernumerary bronchus occurs but rarely. Herxheimer[5] in 1901 reported a true supernumerary "third lung" stemming from the right side of the trachea; Mueller[6] described a similar case in 1918. Brock[7] and others have seen additional examples of a "supernumerary bronchus." On the other hand, the reports of displaced bronchi

have been more numerous. Boyden[3] found one "displaced bronchus" in 400 specimens. Holinger,[8] Huizinga and Smelt,[9] and Brock,[7] mentioned in our bibliography, have observed at least one example of this anomaly.

Holinger and his associates[8] have suggested a simple and useful classification:

1. Normal right upper lobe with 3 normal segments arising above the bifurcation of the trachea.
2. Normal right upper lobe. Abnormal bronchus arising from the trachea.
3. The tracheal evagination consists of only the apical segments (most common).

Fig. 3.—The bronchus arising from the trachea is narrowed at its site of origin.

The pre-eparterial bronchus appears to be associated with an increased frequency of disease in the area of the lung it aerates. Brock[7] studied one case of supernumerary bronchus with bronchiectasis and one with congenital cystic disease in the right lung. Epstein[10] observed a bronchial adenoma in his patient. Holinger[8] noted that one out of his four patients had symptoms. Ferguson

and Neuhauser[11] reported on a patient with a tracheal bronchus with marked irregular stenosis between the tracheal bifurcation and the emergence of the upper lobe bronchus. One of our patients was admitted because of hemoptysis secondary to bronchiectasis in the anomalous bronchus. Some tracheal bronchi are asymptomatic (Gerson and Rothstein,[12] and Brock[7]).

Fig. 4.—Photograph of a bronchogram showing a bronchus arising from the trachea.

This is a report of two men with a bronchus arising from the trachea; the diagnosis was made by bronchoscopy and confirmed by bronchography. In each individual, the right upper lobe showed no apical segment. The proximal branches thus are examples of a "displaced" apical segment. One of the patients presented himself because of hemoptysis. The bleeding came from an aberrant bronchus that was abruptly narrowed at its site of origin from the trachea, (Fig. 3); distally bronchiectatic dilatations were visible. The second patient (Fig. 4) was being investigated because of a so-called "Middle lobe syndrome."

SUMMARY

In man, a bronchus arises rarely from the right side of the trachea. Two patients are presented with this anomaly, both being examples of a displaced apical segment.

Philosophers may take delight in noting that man has lost a bronchus that is present in the sheep and the pig, but what is man's place in nature if that also places him in the class with the cat, the rat, and reptilia?

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